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A PATHOLOGIC STUDY OF THE LUNGS IN ONE HUNDRED AND FIFTY-TWO AUTOPSY CASES OF SYPHILIS*

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PULMONARY syphilis still remains today a doubtful and little explored field for the medical practitioner. Nevertheless, clinical diagnoses of syphilis of the lungs are much more frequently made than they are given a pathologic confirmation at the autopsy table. In view of the apparent increasing interest among clinicians as to the frequency of involvement of the lungs in syphilis, it is of the greatest importance to attack this problem from the standpoint of the new pathologic criteria set up by such investigators as Warthin, Fordyce, and others. This has not yet been done; and the object of this paper is to make an attempt in this direction.

HISTORICAL SURVEY OF PULMONARY SYPHILIS

Morgagni stated that the lungs were frequently injured by the lues venerea. Syphilis of the lungs as a distinct affection, however, was first mentioned by *Zadig*, in a paper published in Jena in 1797. Following this, the main publications upon pulmonary syphilis before 1900 were those of *Bayle* (1810-12), *Munk* (1841), *Guitrac* (1877), *Negri* (1868), *Huchard* (1873), *Frey* (1876), *De Bonilla* (1876); *Poggio, Porter, Samid* and *Nogueire* in 1877; *Lan-*

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*From the Pathological Laboratory of the University of Michigan.

cereaux (1878), *Hanep*, *Sacharjiss*, *Seyler*, *Perry* ("syphilitic fibrosis") before 1890, and *Foulard* in 1893.

The diagnosis of syphilis of the lungs made by these writers, the older ones, as well as the most recent, will not survive any critical examination. Tuberculosis, brown induration of the lungs (once regarded as a syphilitic lesion), chronic lymphangitis (which *Cornil* considered to be syphilitic), gangrene and other conditions were confused with luetic lesions. The diagnosis rested either upon the macroscopic appearances alone, or upon the fact that the pulmonary condition occurred in a person affected with lues. In other cases gross mistakes of diagnosis were made, the conditions described were quite evidently other than syphilis. Among the cases of this class may be mentioned those of *Hedenius*, *Wilks*, *Belin*, *Chrostek*, *Randohr*, and four of the five cases reported by *Tiffany*.

Of other writings upon pulmonary syphilis may be mentioned those of *Lancereaux*, *Landria*, *Parrot*, *Schnitzler* and *Paneritius* befor 1900, *Marfan* in 1901, *Hansemann* and *Kokawa* in 1905. The best collective articles upon the subject are those of *Massia*, *Herxheimer*, *Brandenburg* and *Flockemann*.

An analysis of all the reported cases of pulmonary syphilis reveals the following in so far as frequency, type of lesion, inception and progress of the affection, occurrence of gumma of the lungs, etc., are concerned.

1. *Frequency of Syphilis of the Lungs.*—An examination of the collections and records of pathological laboratories and museums would seem to show that pulmonary syphilis is one of the rarest conditions. According to *Claytor*, in 1905 out of 13,000 specimens at the Army Medical Museum in Washington there was not a single example of pulmonary syphilis. In 1895 in the pathologic collections in London there were but ten cases placed under that label. Neither *Ford* from the Massachusetts General Hospital nor *Otis* in his practice found a single case of pulmonary syphilis. In 6,000 autopsies in Chicago, *Backok* reports but two cases showing syphilitic lesions of the lungs. *Kolisko* of Vienna saw one hundred cases of lung syphilis in thousands of autopsies. *Dorsey* found none in a series of several hundred. *Symmers* found two

cases of "chronic catarrhal pneumonia" due to syphilis in a series of 314 autopsies on syphilitic cases. In 4270 autopsies at the Pathologic Institute in Buenos Aires syphilis of the lungs occurred extremely rarely. In 1911, *Stanley* found two cases of syphilitic pulmonary lesions and one doubtful one among 1,000 cases of pulmonary disease. *Chiari* observed one case of syphilitic lesion of the lung in 98 autopsies on syphilitic subjects. *Osler* saw twelve cases in 280 autopsies on syphilitics at the Johns Hopkins Hospital. *Peterson*, in 1893, found eleven instances of pulmonary syphilis out of 88 cases.

It is evident that the incidence of pulmonary syphilis depends upon the personal criteria of the investigator, the year in which the investigations were made, etc. The multiform variety of the lesions of syphilis increase the difficulty of diagnosis; and these various factors explain the wide differences of investigations, as shown by 61 cases (only one of which was gumma) out of 2,995 of *Stolper*, and the 1 out of 1000 cases of *Hunter*, *Ehlers* and *Wires* giving the lungs the last place as the seat of syphilitic lesions; in striking contrast to this view is the belief of a modern writer, *Rössle*, that syphilis of the lungs is at least as frequent as syphilis of the liver.

If we were to accept the statements of the clinical men, there would be found to be an astonishingly large number of cases diagnosed as syphilis of the lung and the tendency to make clinical diagnoses of pulmonary syphilis seems to be increasing. Undoubtedly many of these cases were given such a diagnosis upon insufficient grounds, and some writers have exaggerated the clinical frequency of pulmonary involvement in syphilis. In four years service under Doctor *Azua* of Madrid, I did not see a single case of pulmonary involvement that could be ascribed to syphilis out of some hundreds of syphilitics. I am inclined to agree with *Dieulafoy* that the clinical diagnosis of syphilis is largely dependent upon the power of intuition possessed by the practitioner. *Stengel* also has stated, to the same effect, that the discrepancies as to the incidence of pulmonary syphilis are dependent upon conditions appertaining to the investigator; the pathologist finds it more rarely than the clinician; the diagnosis of syphilis is more easy and certain at the autopsy. Nevertheless, as *Flockemann* says, there is no good reason why the lungs should not be attacked by lues as frequently as any other part of the body. In more recent cases x-ray examinations have given more assurance to the diagnosis. As far as incidence according to sex is concerned, all writers, as is logical, agree that pulmonary syphilis is more frequent in men than in women, just as they all say that clinical syphilis is more frequently found in the male sex.

2. *Types of Pulmonary Syphilis According to the Authors.*—Two types of lesion, the gumma and fibrosis, are the chief conditions described by the authors, but very different conceptions of these conditions exist among them. Some authors, as *Cornil*, denied the occurrence of pulmonary gumma; others, as *Lagneau*, describe not less than seven different kinds of syphilis of the lung. *Dieulafoy* regarded as syphilitic a bronchopneumonia, cavitary form, fibrosis with bronchial dilatation, and two related forms, gangrene and syphilitic pneumopathy, coincident with pulmonary tuberculosis. To the two main types of lesion, the gumma and fibrosis, accepted by *Mauriac*, *Orth* added an ulcerative and indurative (sclerotic) form. *Neumann* added a "diffuse form;" *Fraenkel* a "catarrhal form;" *Osler*, *Lancereaux* and *Aufrecht* accept the two main types, but the last-named regards the fibrosis as a pneumonia and subdivides it into "interstitial" and "parenchymatous" forms.

More recently new conceptions have arisen, as shown by the terminology applied to the designation of the syphilitic lesions. For example, *Reilly* says that tracheo-bronchitis and profound syphilis are the main forms of pulmonary syphilis; the lesions would consist of gumma or localized or diffuse exudative lesions, leading to fibrosis. Arteritis would always accompany these processes. As to the so-called "syphilitic phthisis," recent authors as *Morris* and *Rössle* accept it, the latter giving as a frequent finding a type of pneumonia resembling the syphilitic "white pneumonia" of the newborn.

All of these classifications with varying terminology are, save rare exceptions, but mere words, and we must agree with *Warthin* that our knowledge of lung syphilis is very incomplete. We are still as in the time of *Pancritius*, or but little more advanced. Said

Pancritius, "Syphilis of the lung consists in a swelling, thickening, hypertrophy, hyperplasia of the interstitial, interalveolar, peribronchial tissues of the lung."

3. *Spirochetes in Lung Tissue.*—The spirochete pallida has been found in the lung of congenital syphilitics by many workers, and is a matter of routine pathologic demonstration; but, as far as I know, the only positive findings of spirochetes in the lung-tissue of acquired syphilitics are those of *Koch*, *Schmorl* and *Warthin*. The finding by *Buchanan* of spirochetes in the sputum of a case of pulmonary syphilis is questionable.

4. *Inception of Pulmonary Syphilis.*—*Dann* of Amsterdam first described pulmonary syphilis precox; and many papers have since been written upon this from the clinical side (*Schnitzler, Schirren, Rothschild, Gwyn, Chantemesse*, etc.). While these writers have discussed the early symptoms and x-ray findings of pulmonary conditions in the second stage of syphilis, no autopsy studies have been discoverable. *Stanley* says that in the first stages of lung syphilis there is a diffuse mediastinitis, with intense cell proliferation filling the alveoli, and infiltrating the septa, peribronchial and perivascular tissues, with epithelial desquamation, giving a gelatinous appearance to the portion of lung involved; in other words, the lesion is a syphilitic acute interstitial pneumonia. In general the opinion of writers upon this subject is represented by *Rössle* who says that the early stages of the lesion are unknown.

5. *Gumma of the Lung.*—The reported case of pulmonary gumma in the literature show an evolution from purely gross diagnostic points to more detailed microscopic descriptions. *Ranvier, Budd, Dumoulin, Wilks, Spencer, Wells, Hutchinson, Jackson, Lebert, Howitz, Hecker, Hertz, Karnbach*, and *Nachs* recorded observations on lung syphilis with descriptions of the gross pathologic anatomy of the gumma. *Cornil, Ranvier, Wagner*, and *Pidoux* attempted to differentiate macroscopically between syphilis and tuberculosis of the lungs. But undoubtedly many of the diagnoses of gumma based upon macroscopic criteria were incorrect; as for example *Hiller's* finding of 9 cases of gumma of the lungs in 87 cases of syphilis.

Lancereaux regarded the multiplicity, size, grayish color, irregular form, firm consistency (slightly elastic), and the inclusion of the gumma in an indurated area poor in vessels, as diagnostic criteria. He accepted also the possibility of expulsion of a gumma per vimus. In *Mannar's* case the diagnosis was made by *Malassez* on the ground of collections of small cells as in gummas of the other organs. *Dessiagou* refers to a case in which many nodules were scattered through a very hard tissue. *Schutz* describes a case with caseation; and *Henop* cases of peribronchial and subpleural caseations, with increase of connective tissue and narrowing of the bronchi. In *Randohr's* case syphilitic pneumonic infiltration and caseation were present; he calls attention to the endarteritis, the vascularization and pleural infiltration. *Pavlinoff* described the infiltration as made up of spindle and round cells without giant cells, the perivascular process being the chief feature. *Nicholson* found calcification but no caseation. In *Salomon's* case the elastic tissue of the lung supported the sclerogummatous tissues. According to *Shingu*, *Störch*, and *Robinson* the arterial lesions form the chief features for the diagnosis. While almost all of the writers mentioned, as well as *Herxheimer* and *Balzer*, found a fibrosis, *Shingu* observed some of the lesions in his case without this reaction. *Hänsemann* accepts the occurrence of regressive changes, while *Hecker* denies them.

Of the more recent writers, *Osler* describes the gummatous lesions as showing minute patches of caseous necrosis in the neighborhood of a vessel showing arteritis. Later there is a capsule formed, and at the same time the pneumonic process develops. Microscopic examination shows the absence of fibrous connective tissue at the periphery, with an infiltration of round cells and an active proliferation. Within the alveoli a cubical epithelium is formed without any giant cells. When giant cells are present they are different from those found in tuberculosis. *Tanaka* and *Patino* give the most modern description of the pulmonary gumma, emphasizing the presence of the plasma cell in the active lesions. All of the recent writers admit the possibility of caseation of the gumma, and some of them, as *Marshall*, accept the possibility of its evacuation through the bronchi. *Claytor* states that the macroscopic appearances of the gumma vary with the stage of its development; it may be a gelatinous mass or nodule of a grayish white color, or yellow, or red, surrounded by a more or less well-defined capsule formed after inflammatory changes.

The great majority of the description of pulmonary gummas were concerned only with the gross appearance. The microscopic de-

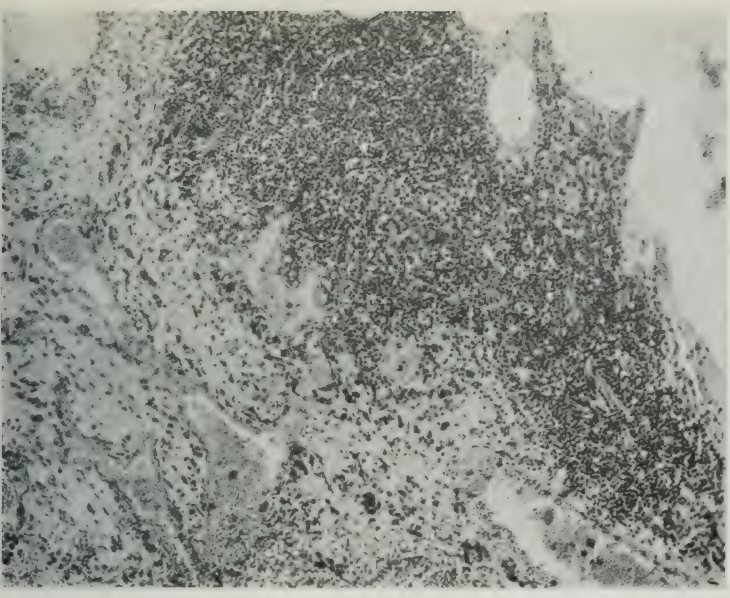

Fig. 1.—Active miliary gumma in lung showing marked syphilitic fibrosis.

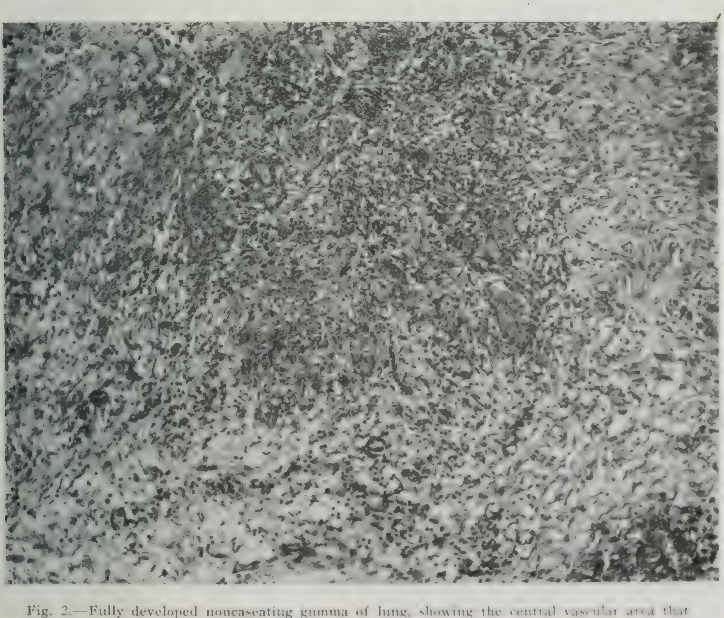

Fig. 2.—Fully developed noncaseating gumma of lung, showing the central vascular area that is just beginning to degenerate.

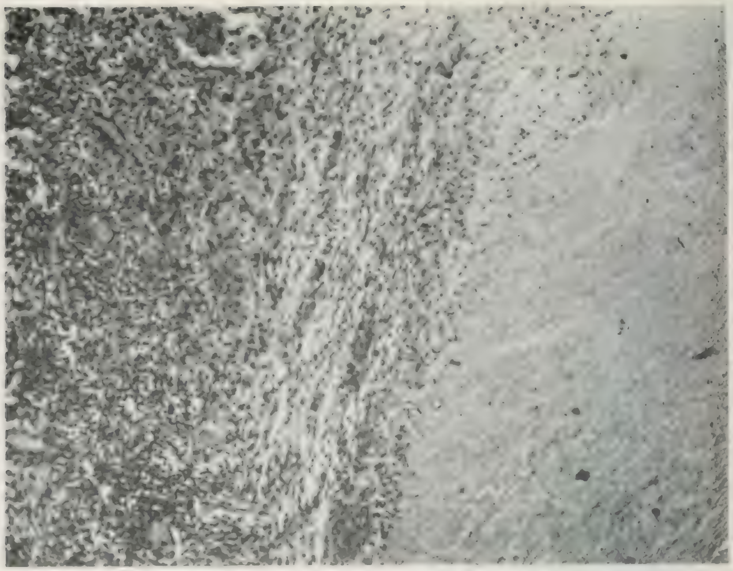

Fig. 3.—Fully developed caseating gumma of lung, showing the three zones.

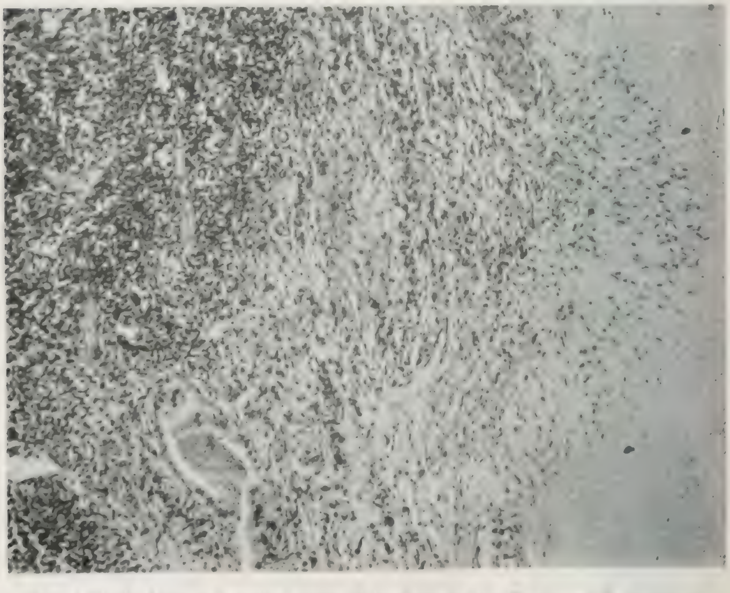

Fig. 4.—Fully developed caseating gumma of lung showing the three zones, the peripheral plasma cell zone being particularly well marked.

scriptions, as a rule, mention the three zones of central degeneration, a caseation, an intermediate one of neoformation, and an outer one of transition or infiltration. It is a very striking fact that in the majority of cases described microscopically the gumma is found in combination with an interstitial fibrosis or sclerosis; there is an accompanying arteritis, a peripheral infiltration of round cells and plasma cells, with a preservation of the yellow elastic fibers in the central zone of caseation. Giant cells are usually few. Of the macroscopic descriptions many are not sufficiently defined to permit any distinction being made between the tubercle and gumma. Some of the points emphasized by the authors as characteristic are the multiple occurrence of the gumma, its subpleural or peribronchial situation, the congestion zone about it, the concomitant pleural thickening, and the extraordinary cicatrization of the lesion.

6. *Location of the Gumma.*—*Hyde* says that a gumma never appears at the apices of the lungs. *Tanaka,* however, admits such a possibility, although the great majority do not appear there. *Kaposi, Brandenburg* and *Rolleston* state that the gummatous lesions are chiefly peribronchial and subpleural; *Fowler,* on the contrary, describes them as in the substance of the lung. All of the writers agree that the right lung is more frequently affected (*Grandidier, Hirsch, Sacharjiss, Pancritius, Pavlinoff, Cube, Salterthwaite, Carlier,* etc.). *Rössle* states that the upper or lower lobes are usually involved, while others (*Grandidier, Cube, Aufrecht*) have found the middle lobe also involved.

7. *Gumma in Congenital Syphilis of the Lung.*—Many writers have described gummatous lesions in the lungs of congenital syphilities (*Apert, Zuber, Martineau, Depaul, Wagner, Lancereaux,* etc.). There may be a combination with white pneumonia, peribronchial sclerosis, or even with tuberculosis. Cases showing all three of these combinations occur in the material of the Pathological Laboratory of the University of Michigan.

8. *Diffuse Syphilitic Pneumonia.*—The literature shows a great deal of discussion over the so-called lobular syphilitic pneumonia of the adult. Some of the cases were examples of syphilitic infection extending from the liver lesions (*Bruhl, Galvagni, Delépine*). The lesions of the lungs, as described, resembled those of congenital syphilitic pneumonia. *Virchow* was unable to differentiate such a syphilitic pneumonia, and the majority of writers have followed

his dictum. *Gambron*, *Grepa*, and others regard it as a simple pneumonia. On the other hand, *Neumann* accepted the existence of a specific pneumonia, and described it as having an acute catarrhal or croupous form, atypical in development and yielding to the treatment of syphilis. *Robinson* also accepts this type of pneumonia, and *Fowler* describes it as a caseous area including many round cells.

Councilman thinks the syphilitic process opens the way for some other infection. *Tanaka* denies the existence of a specific syphilitic pneumonia. *Sokolowsky* says that in many cases a pneumonia due to a different cause is added to the pulmonary process. *Birch-Hirschfeld*, *Roller*, *Orth*, *Davidson* and *Kaufmann* likewise assert that there is not a primary syphilitic pneumonia. *Adami* admits the possibility of a combined pneumonia and pulmonary syphilis.

Among the descriptions given by various authors of combined syphilis and pneumonia is that of *Councilman*, who describes hyaline changes in the capillary vessels, distended alveoli, atrophic alveolar walls and fibrin formation, obliteration of the capillary lumina, new-formed connective tissue around the bronchi and arteries, caseous degeneration, and ultimately fibrosis and sclerosis. Gummas may be present. *Patino* accepts this type of pneumonia, but regards it as a chronic process; when acute he considers it to be due to some other cause. *Witherspoon* describes a form with connective tissue changes, intense cellular proliferation filling the alveoli, with infiltration of the alveolar septa, peribronchial and perivascular tissues. The macroscopic appearances of this form of syphilitic pneumonia are described by *Massia*, as follows: the lung has a gelatinous aspect with one of the lobes hard, heavy, airless, gray or grayish red in color. *Killer*, who was the first to describe this gelatinous appearance, admitted that it could be produced by an interstitial infiltration of the alveolar walls, or by a desquamative catarrhal process; the first he regarded as syphilitic, the second form as due to an added infection. There can be little doubt, I think, that some of these cases, as well as those of *Dieulafoy*, *Raymond* and *Kirchheim* are in no wise different from ordinary pneumonias. Likewise, the descriptions given by *Robertson* and *Aufrecht* of especial types of cells, pigmented giant cells, etc., apply to many early forms of pneumonia, and are not typical of syphilis.

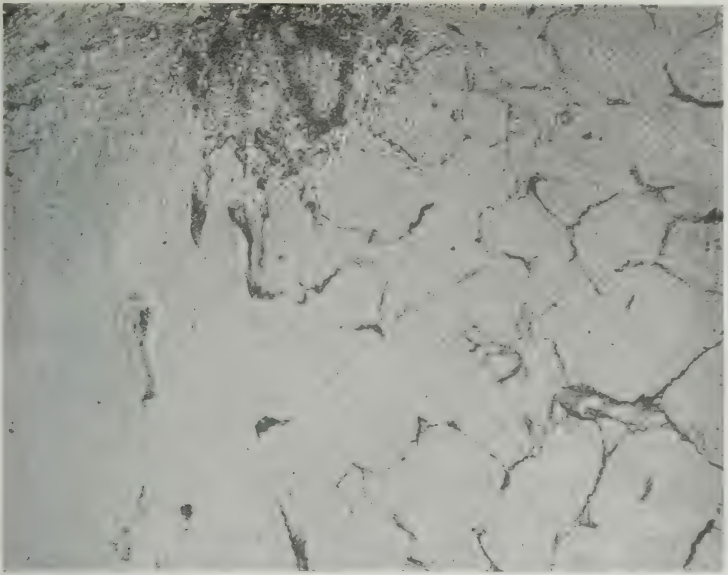

Fig. 5.—Yellow elastic tissue stain of central caseating zone of gumma, showing preservation of the elastic tissue of the old alveolar walls and new formation in blood vessel walls.

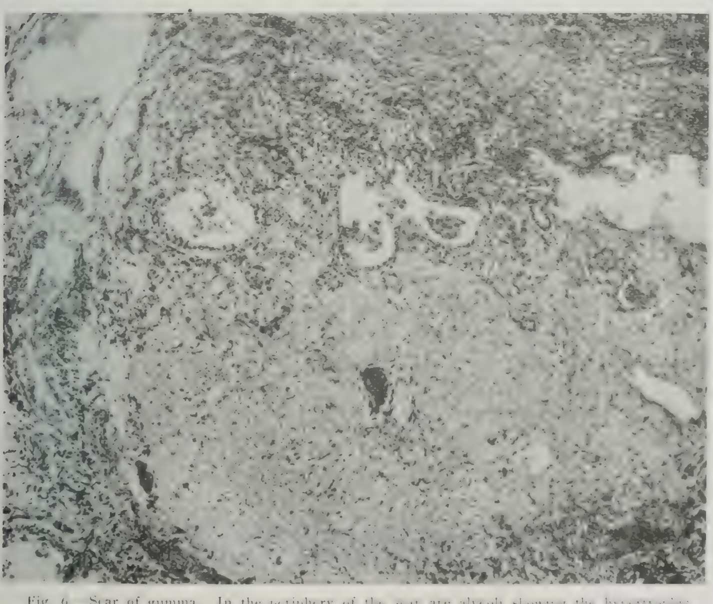

Fig. 6.—Scar of gumma. In the periphery of the scar are alveoli showing the hypertrophic cuboidal epithelium.

9. *Syphilitic Caseous Pneumonia.*—Some authors go much farther, and assert the existence of a typical syphilitic caseous pneumonia. (*Fournier*). (*Councilman* saw a case of this kind in which caseous pneumonia with desquamated epithelium and necrotic cells was associated with hyaline degeneration of the alveoli and endarteritis. At the present time the majority of writers deny the existence of a syphilitic lesion of this type (*Hochsinger*, *Salomon*, *Beriel*, *Orth*, *Tiffany* and *Hertz*).

10. *Lymphangitis Syphilitica.*—Many writers have regarded lymphangitis of the lung as syphilitic in type, as seen by *Weber*. *Hänsemann*, however, demonstrated the occurrence of this lesion in nonsyphilitic cases. It may be in some cases a syphilitic lesion. *Rössle* recently has called attention to the possibility of confusion of this type of lesion with the so-called syphilitic pneumonia.

11. *Muscle Cirrhosis. Brown Induration. New formation of Muscle.*—*Virchow* called attention to the fact that brown induration of the lungs occurs in syphilitics, and he thought the condition might be due to syphilis. The so-called "muskuläre cirrhose" or "carnification" of the lung of the German writers falls in this class. In these conditions the alveolar walls are thickened, and some writers believe that there is a new formation of smooth muscle. *Kaufmann* saw cases which he attributed to syphilis; *Brühl* demonstrated that it occurs in nonsyphilitic cases; and *Davidson* thinks that the *muskuläre cirrhosis* is the result of pulmonary congestion and not due to syphilis. *Tanaka* emphasizes the new formation of smooth muscle fibers near the middle divisions of the bronchi, surrounding the bronchi and the alveoli, and extending into their lumina, and tending to the hardening of the lung tissue, eventually pulmonary sclerosis. *Rössle* says that in one type of syphilitic pneumonia this new formation of smooth muscle is typical (muscular cirrhosis), extending into the alveolar walls and subpleural tissues. *Stöhr* finds smooth muscle fibers normally throughout the lung trabeculæ, but not in the alveolar walls (although present here in the reptilian lung), so that the appearance of this muscle in pathologic conditions is due to a hypertrophy of preexisting fibers, and not to a new formation. *Massia*, *Patino*, and the majority of writers apparently believe in a new formation of muscle in the peribronchial, interalveolar and perivascular tissues, arising either from the bronchial muscle or from that of the hyper-

trophic blood vessel walls. In the latter case it may have no connection with syphilis.

12. *Chronic Interstitial Pneumonia.—Sclerosis.*—As *Patino* has very well stated, syphilis is a disease of chronic evolution and inflammatory reaction, with a tendency to the new formation of connective tissue, particularly in relation to its effects upon the lungs. *Delafield,* in his text-book says that syphilis can be marked in the lung as a diffuse formation of fibrous connective tissue. Even in the time of *Lancereaux* syphilitic scars of the lung were accepted. *Laënnec* in his "Traité de la Auscultation" gave a number of such cases. *Andral, Lancereaux, Greenfield, Gowers* (this case, in my opinion is one of tuberculosis, as shown by the drawings), and *Green* presented cases of this kind. In Green's case the fibroid formation began around the blood vessels, the vascularity of the tissues distinguishing it from tuberculosis. *Pye-Smith* described a case in which contraction of the bronchi was present; and *Mahomed* published two cases with small cell growth and fibrosis; and concluded that many undiagnosed cases might present the same picture. *Osler* thought that fibrous syphilitic bronchitis might be an extension from the pleura. *Weber* reported two cases in which both lungs were fibrosed. *Stanley,* in one of his cases described such a fibrosis without concomitant large gummas as in his other case. Such forms of pulmonary sclerosis have received many names; *Neumann* called it chronic interstitial pneumonia; *Mauriac*, sclerosis of the lung; *Orth*, indurative pneumonia; *Carlier*, hyperplastic sclerosis; *Fraenkel,* diffuse induration. *Virchow* denied that such fibrosis could be ascribed to syphilis. *Ziegler* thought that a part of such conditions might be due to syphilis, the remainder to other causes. This is the prevailing view.

Henske Sforza said that this pneumonia could have a lobar form, but such observation has not yet been recorded. *Massia* described the lung of interstitial pneumonia as showing a fine network of sclerotic tissue, creaking under the knife, and most prominent in the middle lobe in the interlobular trabeculæ. *Hänsemann* describes as typical the ray-like arrangement of the fibers. *Councilman* agreed with *Neumann* as to the form of the "*poumon lobulé*" of the latter author. *Lord* states positively that the picture of these forms of pulmonary fibrosis is not typical of syphilis. The characteristic conditions that have been described as typical are, as follows:

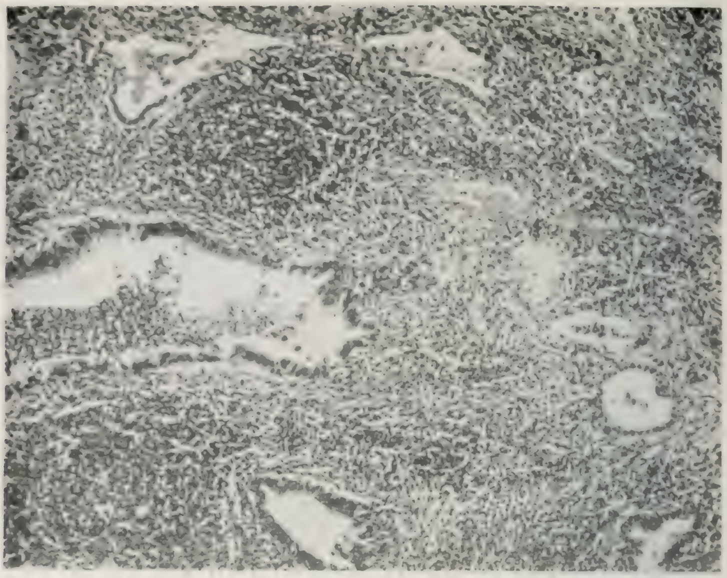

Fig. 7.—[illegible] syphilitic [illegible] with interstitial pneumonia. Marked hyperplasia [illegible] lymph nodes. Diffuse [illegible] cell infiltration and fibroblastic proliferation. Spaces lined with cuboidal epithelium.

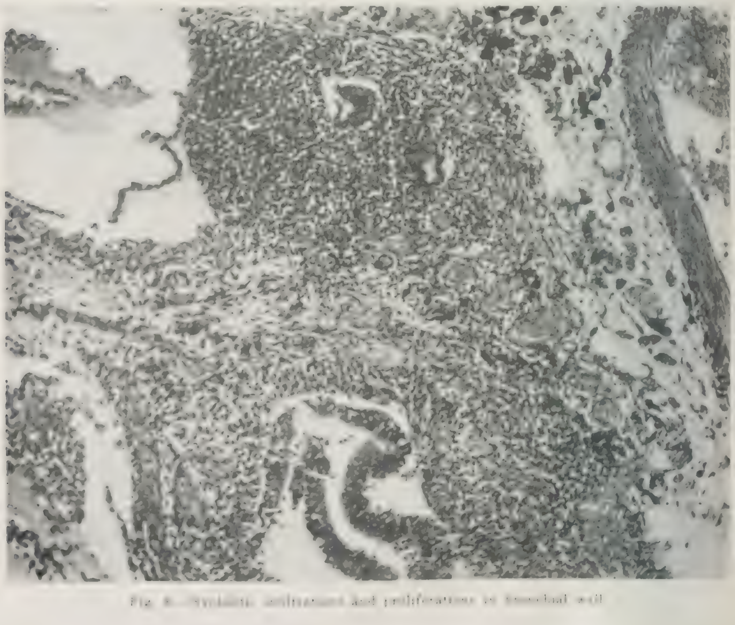

Fig. 8.—Syphilitic infiltration and proliferation in bronchial wall.

a diffuse infiltration localized in the middle portion of the lung, red-yellow in color, of varying shades, smooth, uniform, airless, compact, or nodular with sclerosis of the bronchi, which may be dilated; the sclerotic tissue radiates from the hilum or from the pleura, and can extend to the farthest zones of the lungs; it can form septa of the 3rd and 4th order, giving to the lung a lobulated aspect; the sclerosis is produced by a connective tissue which compresses the alveoli. Round and plasma cells, endarteritis, and perhaps pigmented phagocytes complete the picture; around the bronchi and vessels the thickening is constantly found; and in some places the alveolar walls are thickened. The elastic tissue is very well preserved, and new muscle fibers can be formed along the vessels and in the middle part of the bronchi. All writers agree that the bundles of connective tissue radiate from the pleura, in many cases crossing the lung from side to side.

Pye-Smith regards peribronchial gummas or plaques as the starting-point of the process, and the bronchiectasis as a result. In *Mahomed's* case the remains of a syphilitic infiltration could be seen; giant cells were present. Also in *Rolleston's* case it was easy to demonstrate that the gumma was the first step in the process and *Flockemann* says that this is always the case. The scar tissue can be in isolated patches, or generalized in extensive areas, or diffuse. In many cases, as in *Störch's* the pulmonary cirrhosis alone is evident; in other cases, as in *Petersen's* gummas are present also.

Rössle has lately asserted that the characteristic changes in chronic interstitial pneumonia are peribronchitis and periangitis, thickening of the alveolar walls, increase of pigmentation, and new formation of a network of connective tissue. The lesion affects chiefly the lower lobes; beneath the epithelium there is a new formation of connective tissue; bronchitis with bronchiectasis is present; no secondary collapse of the lung takes place. He affirms that the early stages of the lesion are imperfectly known (in my opinion the picture he gives of such early stages is more like that of early tubercle than of gummatous infiltration). *Rössle* admits the possibility of a macroscopical recognition of the process, because the bronchi appear as white points; the bronchial nodes have a cornified aspect typical of syphilis, with hyaline thickening. The pleura may be smooth, or thickened, the infiltration is most marked about the bronchi, vessels and interlobular septa. In its early stages this interstitial process is recognized with great difficulty. Some writers believe that the earliest stage is a perilymphangitis, as in *Hamann's* case, in which the lymphatic cords were thickened with perivascular new formation of connective tissue which later would result in sclerosis. It is known that the sclerosis is often preceded by gummatous infiltration and subsequent cicatrization. *Stanley* says there are two kinds of pulmonary sclerosis, one in which the increase of connective tissue takes place in the alveolar walls, with miliary gummas, and elastic proliferation forming a thick net-work about the bronchi and pleural vessels; in the second form the lung is contracted, misshapen, without visible gummas.

I must remark here that the writers mentioned above do not differentiate these lesions from those of tuberculosis or anthracosis on a basis corresponding to our actual knowledge of syphilis. Finally, we may consider the "gray induration" of *Massia*, in which were pigmented macrophages (*Mosny*), epithelioid and giant cells of the type regarded by *Nicolas* and *Favre* as not tuberculous in type. Other writers have noted the finding of pigmented phagocytes, but that is possible in different pulmonary processes.

13. *Syphilitic Phthisis.*—There has been much discussion over the existence of a so-called syphilitic phthisis; the earlier authors considered this the only type of syphilitic lesion of the lungs. *Hoffmann* was the first observer; with his findings agreed *Lagneau, Ricord, Graves* and *McCarthey*. *Astruc, Sauvage* and *Morgagni* advanced the possibility that the lesions of syphilis would prepare the way for tuberculosis, and in this way they explained many of the cases. Many authors, as *Sokolowsky*, agree that many of the supposed cases of syphilitic phthisis are in reality tuberculosis. Other writers (*Rollet, Stoicescu, Hänsemann* and *Cube*) admit the possibility of a sclerotic syphilitic tissue with cavern formation, and have described cases of this kind. The pathology of syphilitic phthisis would consist of peribronchial fibrosis, emphysema, fibroid bands, bronchial dilatation, and formation of cavities opening into the bronchi. *Hiller* described a case showing such findings. *Osler* and *Gibson* state that bronchiectatic cavities may be associated with a syphilitic pneumonic process, and that a lung may be ex-

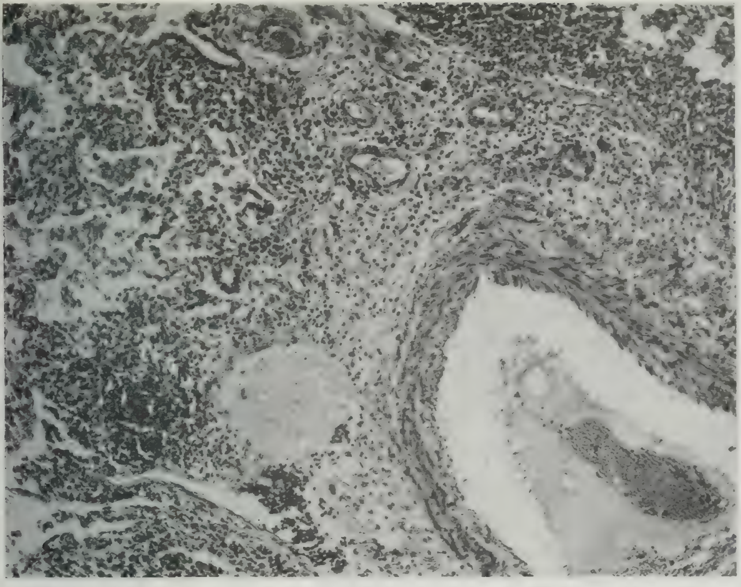

Fig. 9.—Perivascular syphilitic fibrosis and infiltrations in lung. Spaces lined with cuboidal epithelium.

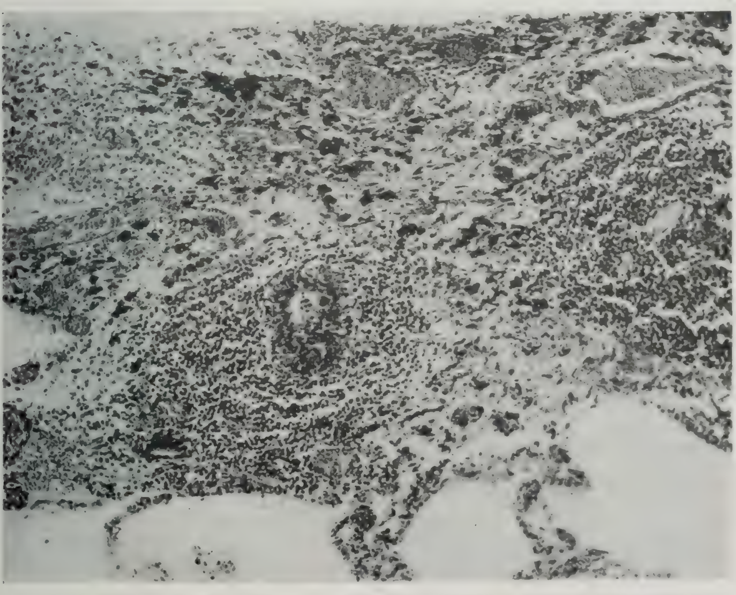

Fig. 10.—Nearly completely obliterated bronchiole due to syphilitic plasma cell infiltrations and fibrosis. Heavy anthracosis in the neighboring connective tissue.

cavated by a bronchial dilatation in the same way as occurs from an aneurysm.

Gangrene of the lung has also been attributed to syphilis. *Caster* has published cases; the endarteritis may be taken as a cause of the gangrene.

14. *Bronchial Lesions.*—The occurrence of syphilitic lesions (thickening) of the bronchi has been emphasized by many writers (*Lancereaux*, *Ewart*, *MacKenzie*, *Kopp*, *Fraenkel*, *Wright*, *Duplant*, *Petersen*, etc.). *Councilman* saw a subepithelial connective tissue increase in the small bronchi with an infiltration of lymphocytes and plasma cells, the new formation projecting into the lumen as polypoid formations rich in blood vessels. Many writers have ascribed a syphilitic origin to bronchiectasis (*Bullrich*, *Grawitz*, *Bronchut*). *Corner* found nine cases of bronchiectasis in 56 cases of syphilis. He attributes the condition to the retraction of the lung tissue resulting from the sclerosis. *Rössle* affirms that syphilitic bronchiectasis is the most frequent form known; associated with the bronchiectasis there would be found the remains of the syphilitic infiltration without giant cells. The anthracotic condition of the lung he considers of great importance. *Patino* found plasma cells in the connective tissue of one case, also the cuboidal cells emphasized by *Tripier*, with endarteritis and periarteritis. Similar infiltrations were found by *Delépine* in one case. In *Beriel's* cases there is an easy confusion with tuberculosis; this he recognized himself. Undoubtedly some of the cases reported are those of congenital syphilis of the lung, although appearing in adults. From tuberculosis the diagnosis is made possible when miliary gummas are present with a syphilitic infiltration (*Rössle*).

15. *Cuboidal Alveolar Epithelium in Syphilis.*—The alveolar epithelium in pulmonary fibrosis or sclerosis often appears as cuboidal, or even low columnar, gland like cells. This has been noted by many observers (*Beriel*, *Dutsch*, *Tripier*, *Farre*, *Gawietz*, etc.). *Tripier* thought they were characteristic of syphilis. *Farre* saw them lining cavities in two cases of pulmonary syphilis; he did not consider them as representing any regeneration of the alveolar epithelium. *Gawietz* saw them in the lung of congenital syphilis. *Massia* found these alveolar new formations in sclerotic tissue of the syphilitic bronchiectasis. Such epithelial new formation may be massive in character, even so large as to form new lung tissue in cases of white

pneumonia (*Robin, Lorain, Malassez* and *Vierling*). *Rössle* regarded them as regenerating epithelial forms in cavities. *Tanaka* noted that in some of his cases some alveoli would be compressed by the sclerotic tissue and would disappear; in others the lumen only would be compressed, and would remain as a mere fissure or star-like opening, in which the epithelium would become cuboidal. *Stroebe, Schultz* and *Spanudis* think that these cells are fetal rests; other writers, as *Hochsinger*, regard them as cells separated by the sclerosis. These cells are found in many different processes (*Kockbart, Beriel, Eppinger, Rössle*). They are common in all chronic fibroid pneumonias, chronic fibroid tuberculosis, etc.; they represent regeneration or hypertrophic alveolar epithelium, and have nothing specifically to do with syphilis.

16. *Syphilitic Lesions in Pulmonary Arteries.*—*Warthin* has given a recent complete review of the reported cases of syphilitic lesions in the pulmonary arteries, reporting a case of his own with aneurysm of the artery and demonstration of spirochetes in the wall of the aneurysm. Gumma of the pulmonary artery has been reported by *Weber, Wagner, Sequiera* and *Hanford;* gummatous arteritis by *Schwalbe, Kasem-Beck, Wagner* and *Quiatkowski*, and *Winternitz* and *Schmeisser;* nongummatous arteritis by *Thorel, Henschen, Rogers, Dickinson, Payne, Wallace, Friedrich, Grigorjew, Loveland, Brüning, Wagner* and *Quiatkowski, McPhedran* and *MacKenzie, Ribbert, Westenhoeffer*, and *Brooks*. Cases of aneurysm of the pulmonary artery with suspected syphilitic etiology occur in the literature, but *Warthin's* case is the first one in which this etiology has been positively demonstrated. *Birch-Hirschfeld, Greenfield* and *Petersen* have described the vascular changes in pulmonary syphilis as a meso- and endarteritis. *Pavlinoff* found vessels with obliterated lumina. *Lindwahl* gave a great importance to the endarteritis of the small arteries. *Sugai* states that in syphilitic arteries of the pulmonary vessels the middle coat is chiefly affected, together with the adventitia. *Kokawa* emphasizes the point of origin of every gumma around the vessels; he could see no difference between the arterial changes in tuberculosis and those in syphilis. *Warthin's* study has shown that syphilis of the pulmonary artery is essentially a mesarteritis and periarteritis, with histologic features identical with those of syphilitic mesaortitis.

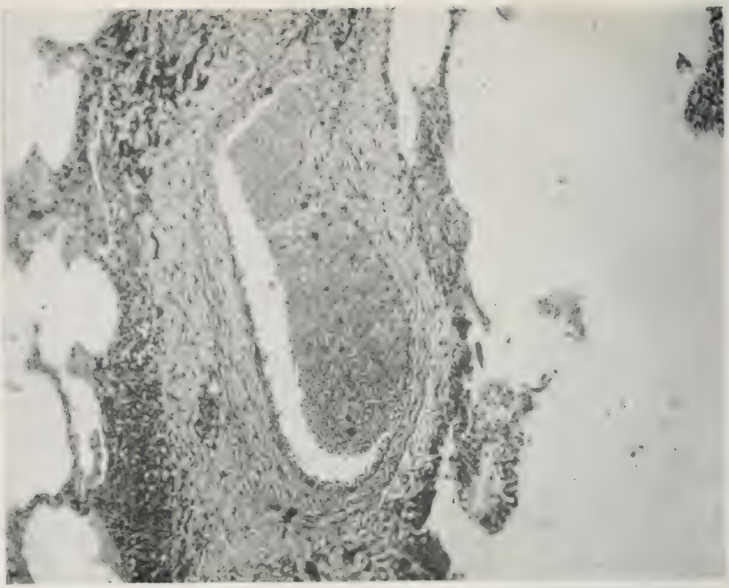

Fig. 11.—Syphilitic lesions in small pulmonary artery.

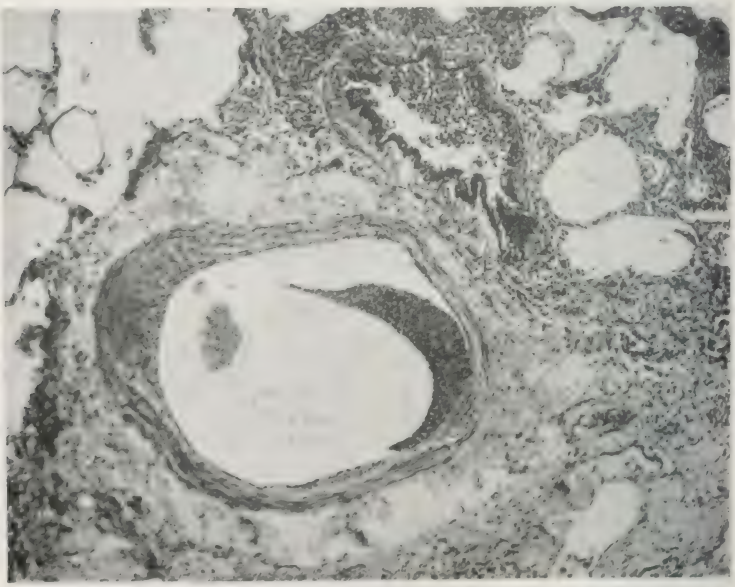

Fig. 12.—Changes in small artery and neighboring tissues in syphilis of the lung.

17. *Lesions of the Pleura.*—The older authors believed in the existence of a specific syphilitic pleuritis (*Lancereaux*). (*Orth, Hänsemann* and *Rolleston* reported cases with thickened pleura. *Raymond* accepted the existence of an exudative syphilitic pleuritis. *Sadowski* saw a case of gumma of the pleura; *Renbier, Gerest* and *Wies* observed cases with pleuritis; but the appearances were in no way different from those of other forms of pleurisy. Likewise, in the cases described by *Massia, Rössle* and *Sugai* no characteristic appearances of syphilis are recorded.

18. *Anthracosis and Syphilis of the Lung.*—*Filadoro* and other writers have noted the frequency of excessive anthracosis associated with lung syphilis; particularly in the peribronchial nodes is the anthracosis marked. *Osler* and *Rössle* have also remarked upon the pigmentation in their cases.

19. *Elastic Tissue in Pulmonary Syphilis.*—Many authors agree as to the persistence or even increase of yellow elastic tissue in syphilis of the lung, particularly in the cases of syphilitic sclerosis. The increase is especially marked in the vessel walls.

20. *Syphilis and Tuberculosis.*—The older writers undoubtedly classed many cases of tuberculosis as syphilis. *Mauriac* and *Petain* were the first to attempt a differentiation, but the majority of writers emphasize the difficulty attending both macroscopic and microscopic differentiation. *Hertz's* opinion that the gumma of the lung can not be diagnosed macroscopically still holds good with the majority of pathologists today. *Virchow,* on the contrary, said that the macroscopic diagnosis was the only possible way, as microscopically he regarded the tubercle and gumma as having the same appearances. *Birch-Hirschfeld* declared that the only sure method of differentiating was the demonstration of the tubercle bacillus. Other writers insist upon the formation of fibrous connective tissue extending from the hilum along the bronchi and vessels as a certain indication of syphilis, (*Lindwahl, Downing*). The fibrous nature of syphilis is emphasized by many (*Goodhalt*). The occurrence of gummas around the main bronchus is considered by *Massia* as an important sign. According to *Fournier* the characteristics of the gumma are their unilateral occurrence, relative scarcity, nonconfluence, nontransparency and elastic consistence. The microscopic differentiation according to *Ziegler* rests upon the scarcity of giant cells and

the new formation of blood vessels in the periphery of the gumma. According to *Kaufmann* the gumma is characterized by its non-calcification and by the presence of plasma cells. *Fowler* observed calcareous deposits in gumma of the lung. *Stanley* holds that the proliferation of the elastic tissue is greater in syphilis than in tuberculosis. *Hänsemann* considers the formation of granulation tissue as characteristic of syphilis. In general, the main points of differential diagnosis of gumma and tubercle, as obtained from the literature, are the rich vascular formation, the grouping in a mass rather than in small nodules, the scarcity of giant cells, and the infrequency of calcification, together with the preservation of the pulmonary architecture, in syphilis.

As to the etiologic relationships of the two diseases there is a widespread belief that a syphilitic lesion of the lung prepares the way for a tuberculous infection, and aids in its spread. (*Brock*, *Power*, *Potter*, etc.). Other writers believe that a tuberculosis also acts as a spur to syphilis (*Schnitzler*, *Schlecht*, *Guerin*, *Gouget*). Other writers believe that this not infrequent combination is purely a coincidence (*Balzer*). According to *Sergent* and *Rindfleisch* syphilis of the lung makes fibrous a secondary tuberculosis. *Leredde* has more recently emphasized the importance of latent pulmonary syphilis in causing sclerosis of the bronchi and thus producing a predisposition to tuberculosis. Many cases of syphilitic lesions of the lung might thus easily escape clinical detection and be covered up by a tuberculosis.

21. *Giant Cells in Syphilis.*—Much discussion has centered about the importance of giant cells as diagnostic factors between syphilis and tuberculosis. Many writers have noted their occurrence in their cases (*Tanaka*, *Askanazy*, *Scheib*, *Patino*, *Bade*) ; others have not (*Sugai*) ; and other writers say that true giant cells do not occur in the syphilitic lesion, but only false giant cells. *Baumgarten* considered the presence of giant cells as meaning always tuberculosis, while *Hause* says they are always present in the lesions of syphilis. Today the majority of writers agree that they occur in both diseases, although usually more abundantly in tuberculous processes; and that there is no difference at all in these cells as found in both conditions.

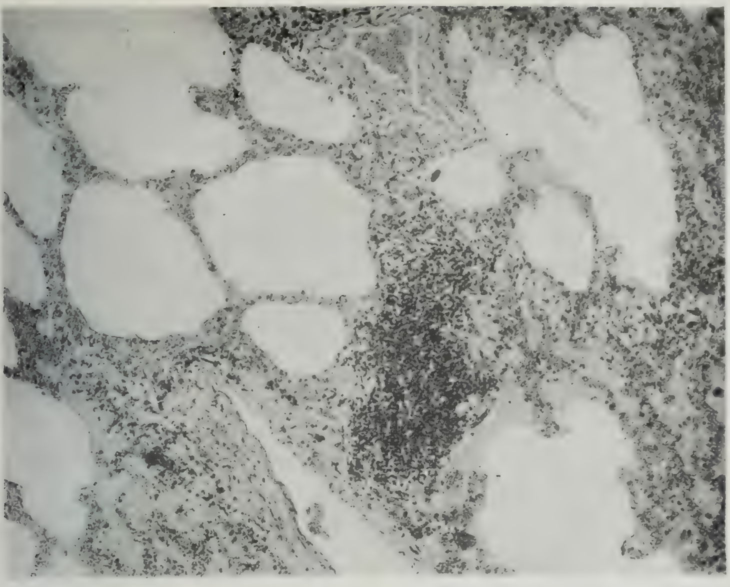

Fig. 13.—Diffuse syphilis of the lung with irregular fibrosis and patches of plasma cell infiltration. In this lung every stage between these small infiltrations and fully developed gummas was found.

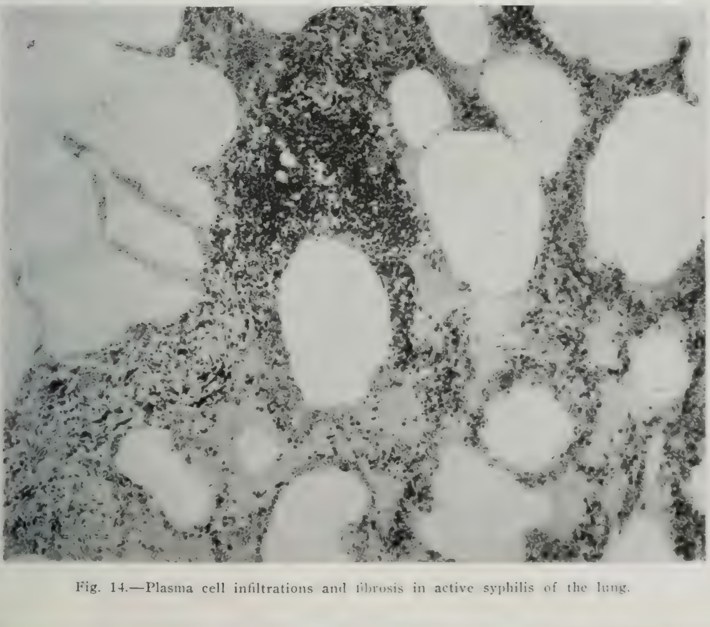

Fig. 14.—Plasma cell infiltrations and fibrosis in active syphilis of the lung.

II. RESULTS OF THE STUDY OF THE LUNGS IN 152 AUTOPSY CASES OF SYPHILIS

From the above study of the literature it will be seen there is very little that is definitely known about syphilis of the lung, aside from the relatively infrequent cases of pulmonary gumma. We know today from the work of *Warthin* that the gumma is a relatively rare lesion of syphilis, and that the essential pathology of syphilis, as it affects the central nervous system, heart, aorta, liver, pancreas, adrenals, testis and other organs, is a mild inflammatory process characterized by lymphocyte and plasma-cell infiltrations, leading eventually to fibrosis and atrophy. Such modern pathologic criteria, together with intensive search for the *Spirochete pallida*, have not yet been applied to the problems of pulmonary syphilis. Undoubtedly the difficulties attending the study of syphilitic changes in the lungs are greater than in the case of other organs, owing to their peculiar structure and the great frequency of other pathologic processes that may obscure the syphilitic process. The most logical way of getting at the matter, it would seem, would be to study thoroughly microscopically the lungs taken at autopsy from syphilitic cases. This has not yet been done, and we do not know to what extent the lung shares in the minute inflammatory changes that occur in the other organs in every case of syphilis examined. At Professor *Warthin's* suggestion I have undertaken such a study of the lung in known cases of syphilis. One hundred and fifty-two cases were selected from the autopsy material of the Pathological Laboratory of the University of Michigan in which an undoubted diagnosis of syphilis had been made from the presence of specific syphilitic lesions in other organs and tissues. These cases included (about one-third) those that had been clinically diagnosed as syphilitics before death, including paretics, tabetics, aortic aneurysms, syphilitic myocarditis, aortitis, hepatic syphilis, gummas of brain, lungs, liver, bones, skin and testis, salvarsan poisoning (5 cases), and other clinical forms of syphilis. The remaining cases were those in which a clinical diagnosis of syphilis had not been entertained in connection with the patient's terminal affection. In these the diagnosis of syphilis rests upon anatomic signs of syphilis alone, or upon a combination of anatomic lesions and the demonstration of the spirochete.

The material was, for the greater part, formol fixed, paraffin imbedded, and stained with various stains, chiefly hematoxylin and eosin, Weigert's elastic tissue method, Kresylecht-violett, Van Gieson's and the Levaditi method. Blocks were taken from the two lungs and from different portions of the lobes; but even with this work the amount of lung tissue examined is relatively very small. Negative findings can not, therefore, be taken as absolutely indicative of all parts of the lung, inasmuch as the areas of active lesions of syphilis may be sharply localized in certain portions, and may be entirely missed. Our experience in searching for active areas in such organs as the heart and aorta has taught us that in some cases it becomes necessary to take many blocks of tissue and cut many thousands of sections before active lesions are found. Much more necessary is this with the Levaditi method in the search for spirochetes. So time-consuming is this that I was able to apply it to ten cases only, making four blocks of each case and cutting the sections at eight different depths. Negative results under such conditions may be wholly the result of the inadequate search.

As the result of this study I found in 12 cases out of the 152 histologic changes in the lungs that I regard as undoubted syphilitic lesions, as follows:

1. Gumma of the Lung	3 cases
2. Syphilitic Peribronchitis with Arteritis	2 cases
3. Syphilitic Fibrosis with Arteritis	4 cases
4. Syphilitic Arteritis	3 cases
Total	12, approximately 8 per cent.

These diagnoses were made upon the modern histologic criteria for syphilitic lesions as given in the Harvey Lectures for 1915 and 1918 by *Fordyce* and *Warthin* respectively.

Gumma of the Lung.—In one case the diagnosis of pulmonary gumma was made macroscopically by *Warthin* at the autopsy table and confirmed microscopically. There were pleural adhesions, some fluid in the cavity, and a number of pigmented nodules under the pleura. Both miliary noncaseating and larger caseous gummas were found throughout the lungs. Microscopically, the caseous gummas showed three distinct zones, a central caseous area, an intermediate fibrous zone with many new blood vessels, and an outer vascular, infiltrated zone rich in plasma cells and lymphocytes. In some of the gummas the outer zone is very broad and diffuse, disappearing gradually in the thickened walls of the bordering alveoli, while others have a more discrete border, but never as sharply circumscribed as the edge of a tubercle. The lung tissue at the periphery of the gumma is compressed and pushed away, but does not show any especial characteristics. Rarely do the gummas touch each other and form a continuous mass; they do not become confluent as do miliary tubercles. The tissues surrounding the smaller gummas often show a heavy deposit of anthracotic pigment. The central caseous zone presents the appearance of a coarsely granular caseation in which few nuclei in varying stages of karyorrhexis are seen. The outlines of capillaries containing blood cells and fibrin can still be made out. There is no fibrin presented in the caseous area except in these vessels, in contrast to the fibrin threads so abundantly found in the caseous centers of tubercles. The intermediate fibrous zone is made up either of young fibrous tissue or an older, more hyaline form, but never distinctly epithelioid, as in the tubercle. Fibroblasts appear, and great numbers of angioblasts in the form of cords or young capillaries containing blood cells. This zone usually shows many plasma cells and lymphocytes, and these increase in number in the outer infiltrated zone, which may appear to be made up almost entirely of plasma cells, but capillary proliferation and increase of stroma can always be made out in this zone. The larger blood vessels in part show the picture of syphilitic endarteritis, particularly when the vessels appear to be the starting place of the gummatous process. Other vessels show hyaline change. Many very small infiltrations of lymphocytes and plasma cells, with occasional endothelioid cells occur. There may be very young miliary gummas or simple syphilitic lesions. In some cases it is very difficult to differentiate these, when taken alone, from hyperplastic rudimentary lymph nodes or young tubercles. In some cases it may be impossible to do this, as other writers have affirmed, and the diagnosis rests upon the more completely developed lesion. As such lesions will nearly always be found in connection with the younger ones, there will practically never be any difficulty in making a differential diagnosis of syphilis. Giant cells exactly like those of tubercles, with peripherally arranged nuclei were present in this case, but not so numerous as is usual in tuberculosis.

The gumma, even the youngest form, is essentially a vascular lesion, built up largely of angioblastic proliferations infiltrated with plasma cells and histogenetic lymphocytes. As the new formed vascular tissue develops, its vessels in part become obliterated or thrombosed, the connective tissue more hyaline, the cellular infiltration less, and at last the older central part caseates or becomes fibroid. Typical changes appear in the medium and larger vessels of the part, proliferation of the external and internal coats, degenerative changes in the intima and middle coats, with plasma cell infiltration.

In the caseous area the alveolar structure may at times be preserved; yellow elastic tissue is usually present, both of the alveolar wall and of the blood vessel walls, although its amount may be reduced. At the periphery the amount of elastic tissue may be increased in places, in others it may disappear; the fibers may be short and thick as in degenerating elastic tissue. In some gummas the elastic tissue may disappear entirely in the caseous zone, and no elastic tissue appears in the new formed vessels. Around some vessels the elastic tissue appears degenerated, forming irregular masses staining poorly. In some of these areas there is a proliferation of spindle cells infiltrated with small cells. In general the elastic tissue is better preserved than in tuberculosis. Some vessels show a collagenous degeneration. The epithelial proliferation in the alveoli described by some authors was not present in my case. A striking difference from tuberculosis is shown in the gradual transition of the lesion to the neighboring tissues. The scars of the healed gummas are very characteristic. They are never round, but have an irregular form with extensive ramifications, and are vascularized. Around the borders of the recent scars remains of the syphilitic infiltration may still show. Staining for spirochetes negative. Patient had clinical history of syphilis.

In the other two cases of pulmonary gumma the diagnosis was not made macroscopically, one of them showing small noncaseating gummas, the other gummas in the stage of cicatrization. The first of these cases showed the same microscopic pictures as did the smaller gummas in the case just described. Giant cells were present. There was an extensive zone of fibrosis beneath the pleura. This showed lymphocyte infiltration with abundant anthracosis and scattered miliary gummas. The tissue showed much new formation of blood vessels. Zones of vascularized fibrosis started beneath the pleura and extended through the lung. In these connective tissue trabeculæ remains of the syphilitic infiltration are present in areas. No mast cells were found in these infiltrations. Yellow elastic tissue was absent in the fibrosis. The smaller vessels showed no syphilitic changes. Tissues from this case were not stained for spirochetes.

The third case of healing gumma coincident with a hepar lobatum showed the same essential histologic picture as in the first case. Masses of sclerotic tissue surrounded some of the bronchi; this contains in many places remains of the syphilitic infiltration, and small nodules of plasma cells (miliary gummas). The scar of the large healing gumma is stellate, showing a peripheral plasma cell infiltration, vascularization and pigmentation characteristic of the gummas in the other two cases. Through the scar some elastic fibers can be found; at the border they are more abundant and occur in groups of fibers, in some cases preserving the contour of the vessel wall. The larger blood vessels show syphilitic arteritis. In some of the bronchi surrounded by sclerotic tissue there is a marked proliferation of the bronchial epithelium, almost obliterating the lumen. This case was not stained for spirochetes.

Syphilitic Fibrosis of the Lung.—A very marked fibrosis was found in 18 cases out of the 152; a well marked condition of brown induration was found in 43 cases; while an increase of connective tissue associated with chronic passive congestion was present in 124 cases, or 82 per cent. These findings are very striking, and are in general accord with the changes produced by syphilis in other organs (fibroid heart, arterial sclerosis, chronic interstitial pancreatitis, chronic fibroid orchitis, etc.). The question, of course, is to what extent this fibrosis is the result of the direct localization and action of the spirochetes in the lung tissues, or how much of it is purely secondary to the damaged heart and its enfeebled action. Are these lungs showing an increase of connective tissue the seat of a syphilitic inflammation, or is the fibrosis the result of a chronic passive congestion? Are these lungs purely cardiac lungs?

At the beginning we must insist upon the fact that the fibrosis due to syphilis takes its inception in a typical inflammatory process due to the local action of the spirochetes; and *unless this infiltration is shown we can not make a positive diagnosis of syphilis.* Fibrosis is the termination, the sequel, of the syphilitic process, and it is only the active area of inflammation that presents specific characters by which we can diagnose it positively, although certain characteristics of the syphilitic scar may at times aid greatly in the diagnosis. *From the syphilitic inflammatory infiltration proceeds a fibrosis which should extend along the vessels and bronchi as well.* The syphilitic process may, however, be masked by other processes (tuberculosis, pneumonia, gangrene, etc.).

The connective tissue formation in the lungs of 60 cases of tuberculosis was studied in comparison with the syphilitic lungs. This study convinces me that it is never impossible to distinguish the fibrosis of tuberculosis from that of syphilis, no matter how difficult the case may be. The earliest lesions of pulmonary syphilis may escape our notice more easily than the early tubercle; and there can be but little doubt that many syphilitic lesions of the lung do escape our notice pathologically. The formed gumma and the developed tubercle can be readily distinguished by the avascular, closely packed, epithelioid, sharply circumscribed, conglomerating character of the latter, while the gumma appears as a more loosely arranged, less sharply delimited, vascular granulation tissue, scant in epithelioid and giant cells, and infiltrated with lymphocytes and plasma cells. The scar of the tubercle is round, sharply delimited, with concentric fibers, hyaline, scant in nuclei, devoid of vessels and elastic tissue, less given to anthracotic pigmentation, but more frequently calcified, and very often confluent or conglomerated. The scar of syphilis is irregularly radiating or stellate, not sharply delimited, more like ordinary cicatricial tissue, still contains blood vessels, often with angiectatic capillaries, continuous with the thickened walls of the nearest alveoli, still shows elastic fibers, and the outlines of old vessels and alveolar walls; the scars of gummas are extremely rarely conglomerated or confluent; the syphilitic fibrosis begins under the pleura and around the bronchi, and is more frequently anthracosed, and very rarely calcified. But the most conclusive differential point is the finding in the fibrosis of syphilis of collections of plasma cells, and such active areas are probably as frequent in syphilitic fibroses of the lung as they are syphilitic processes elsewhere in the body.

Likewise, the syphilitic lesions of the vessels, when found, are so typical that they alone will fix the diagnosis. I have to state here that I do not agree with many of the text book pictures of syphilitic arteritis in the lungs, as the conditions pictured may exist in the absence of syphilis. Although some writers say that a differential diagnosis can not be made between the vascular changes in pulmonary tuberculosis and those in pulmonary syphilis, I am convinced that such a differentiation can be made. In tuberculosis the endarteritis and the periarteritis are of one character; all three coats of the vessel are attacked in a massive way, while in syphilis the middle coat may show no alteration. This is in opposition to *Lindwahl* who states that in syphilis all three coats of the vessel are attacked massively. I hold that this is not true of the syphilitic process. The proliferation of the intima and the obliteration of the lumen may be alike in some cases; the vessel lumen may be obliterated by the pressure of a gumma, as well as of a tubercle. The descriptions in the text books of the obliteration of the lumen by its being pushed to one side by proliferation of the internal coat are typical of syphilis. In tuberculosis no coat of the vessel is respected; in syphilis the vessel may show an intact middle coat. The infiltration of the inner coat by round cells is most marked in syphilis and the elastic tissue is better preserved; proliferation of elastic tissue takes place in the internal coat in syphilis and not in tuberculosis; the middle coat is better preserved and its muscle often hypertrophic and well differentiated. In tuberculosis the elastic coats disappear or are degenerated, and the muscle fibers of the middle coat may disappear or show atrophy or degenerative changes. Cellular infiltration of the middle coat means syphilis; if the adventitia shows plasma cell formation, new capillaries and new formed elastic tissue, the process is syphilitic. Tuberculosis causes massive changes in the vessels from the outside; syphilis coat by coat regularly. Hyaline change in the smaller pulmonary vessels may occur in either process.

Still more difficult is the differentiation of syphilitic fibrosis and that of chronic passive congestion, particularly the more severe forms of brown induration. It must be borne in mind that *Virchow* and other writers have considered brown induration and the heart lesion cells as syphilitic lesions. It is a striking fact that 28 per cent of our autopsy cases have shown a typical brown induration of the lungs, and 82 per cent have shown the pulmonary changes of chronic passive congestion. In comparison with these cases we examined the lungs of 100 successive autopsy cases that showed no lesions of syphilis and found only 5 per cent showing this lesion. Nothing could better illustrate the effects of syphilis upon the heart and the secondary results upon the lungs. The coincidence of the brown induration, the typical heart-lung, is due to the fact that can not be too often repeated that syphilis is the most important etiologic factor in cardiac (myocardial) disease. Therefore, if an autopsy case shows a well-marked brown induration the chances are greater for its association with syphilis than with any other condition.

The general appearances of the fibrosis of brown induration and of syphilis are very much alike; the existence of the anthracotic border is common to both. The essential differences rest in the typical vascularization and infiltrations of syphilis. In the connective tissue of syphilitic fibrosis the small diffuse or focal collections of lymphocytes and plasma cells, with or without typical gumma formation, and associated with characteristic vascular changes make possible the differential diagnosis. The vascular changes due to the chronic passive congestion, dilatation with hypertrophy of the coats, and often hyaline change, may in part obscure the syphilitic vascular changes. Even in the combination of syphilis, tuberculosis, and brown induration the differential points can be found on careful search. The fibrosis of brown induration follows the vessels, radiating from the hilum; it is more regular than that of syphilis, and does not show the stellate radiations characteristic of the latter. So far as the fibrosis is concerned the yellow elastic tissue stain offers no aid in the differential diagnosis of syphilis and brown induration; but it does in the case of the vascular changes. In the nonsyphilitic cases no infiltration is found at the periphery of the vessels. The occurrence of connective tissue bundles outside of the vessels, their vascularization and evidences of plasma cell infiltration are the essential diagnostic points by which the fibrosis of syphilis may be distinguished from that of chronic passive congestion. As practically every lung of syphilitic fibrosis is also a lung of chronic passive congestion, the differential diagnosis requires a thorough and careful histologic study for the determination of these points. If the syphilis is active the diagnosis may be easily and quickly made, but in old latent cases extensive search may be necessary to locate characteristic lesions.

The presence of the cuboidal cells of *Tripier* does not favor the diagnosis of syphilis, as they are found in any chronic fibroid process in the lung (tuberculosis, actinomycosis, chronic fibroid pneumonia, etc.). Further, the idea quite commonly held that the folding in of the elastic tissue coats in the vessels is a sign of syphilis is not correct. This lesion is not confined to syphilis, but may be found in sclerosis due to other causes. Aside from the characteristic infiltrations of the vessel wall the good preservation of the middle coat is a feature confined to syphilis. The classical descriptions of syphilitic arteries in the text books no longer apply, in as much as nonsyphilitic cases may show the same changes. It is possible to regard as syphilitic only those vascular changes described above. The classical splitting of the elastic coats is not confined to syphilis; endarteritis without the cellular infiltration of the vessel coats is not syphilitic. Proliferation of the elastic coat inside the internal elastic is not characteristic of syphilis. Blood vessels with typical syphilitic infiltrations show little change in the elastic tissue. The increase or hypertrophy of the muscle of the vessels does not take place in syphilis at all, or to a degree so slight that it is not recognizable. In brown induration such muscle changes are marked in the vessels.

Pleura in Syphilis of the Lung.—While chronic adhesive pleuritis, old pleural adhesions and thickenings were common findings in these cases, no characteristic changes of syphilis were found in the pleura.

Bronchial Lesions in Syphilis.—Typical active syphilitic peribronchitis was found in two cases. In one case associated with marked syphilitic lesions of the brain, aorta, heart and testes, the peribronchial tissues showed a beautiful plasma cell infiltration, with new-formed vessels, formation of a vascular connective tissue around the infiltration, with heavy deposits of anthracosis. In many places the infiltrations are nodular (miliary gummas). The bronchial epithelium is well preserved. The alveolar walls showed nothing characteristic. Patches of sclerosis occurred throughout the lungs. In the peribronchial connective tissue spaces lined with the cuboidal cells of Tripier were present. The vessels showed a typical syphilitic picture, with plasma cell infiltrations in intima and adventitia. New-formed muscle occurs in connection with the bronchi, but not in the vessels. The elastic tissue of the bronchus is either destroyed or pushed away at the seat of the infiltrations, often appearing on the outside as thick, short, broken fibers, or as bundles of new-formed elastic fibers. These changes affected all parts of the two lungs. One lobe showed the condition of a gray hepatization of croupous pneumonia, the immediate cause of death. No spirochetes were found in the lung.

In another cause the lung showed marked sclerosis of the blood vessels with proliferations of the intima not of the syphilitic type, but with typical syphilitic infiltrations of the inner and outer coats. Typical syphilitic infiltrations existed around the bronchi with new-formed muscle and connective tissue. The muscle coats of the bronchi were greatly thickened, and the cuboidal cells of Tripier were found in peribronchial spaces. Scattered areas of vascularized granulation tissue infiltrated with plasma cells occurred throughout the lungs, particularly beneath the pleura at the lung borders.

In no other cases were typical syphilitic lesions of the bronchi found, although the latter showed frequently various conditions that different authors have regarded as due to syphilis. We were not able to find syphilitic changes in the lungs associated with bronchiectasis. Tripier's cuboidal cells occurred in many cases without syphilitic changes being found. My experience is different from that of *Rössle* who so frequently found remains of infiltrations in sclerotic peribronchial tissues. In these cases no evidence of congenital pulmonary syphilis was found that could be recognized as such except in two cases in which other organs also showed the lesions of congenital syphilis. These cases did not show the proliferation of alveolar cells described by *Rössle.* The differential points between congenital and acquired pulmonary syphilis in adults, as given by *Rössle* do not hold. The differential point as to the anthracotic border around the congenital areas does not hold; and it is impossible in the adult to distinguish between congenital and acquired pulmonary syphilis.

Mucous Glands.—No changes were found in the bronchial mucous glands.

Lymph Nodes.—In one case, associated with marked syphilitic mesarteritis of the large pulmonary arteries with aneurysm of a main branch in the upper left lobe the peribronchial lymph nodes showed marked typical syphilitic vascular formations and thickenings, with plasma cell collections. Spirochetes were found in the artery, the aneurysm wall and the peribronchial infiltrations in this case.

SUMMARY

The study of the lungs of these 152 cases gives us 12 cases diagnosed positively as syphilis upon the criteria described above. The cases fall into two groups: 1. Gumma, with peribronchial lesions and arteritis, five cases falling into this group, three of them in the first subdivision; 2. Fibrosis and arteritis, embracing seven cases, three showing definite syphilitic processes in the vessels alone.

If we compare these findings of active syphilitic lesions in the lungs with those found in the other organs of the same cases we are struck by the great disproportion. The heart and aorta of every case showed typical active infiltrations, the testes of every male showed the same, the great majority showed active lesions in pancreas, adrenals and liver, and those cases in which the central nervous system was examined showed a high incidence of syphilitic lesions. Upon what grounds does the apparent greater freedom of the lungs from such lesions rest? Is the lung actually more immune to syphilis and less frequently involved in the mild inflammatory processes that are always found in other viscera? I do not think so; it is very probable that many other lungs were syphilitic, but the specific active changes were not found; and it is only upon these that we can make a positive diagnosis of syphilis. The examination made is, of course, very incomplete; only a limited amount of lung tissue was routinely preserved from the autopsies, and it was possible to examine only a small part of this tissue. The portions examined represent a very small area of the lungs as a whole; and the chances of missing such changes as are produced by syphilis are infinitely greater than of finding them. Further studies of this kind, much more intensive as to the amount of lung tissue examined, are needed before we can pass judgment upon the importance and frequency of syphilitic lesions in the lung. It seems most probable that the lungs are involved in the mild general infection of syphilis to about the same degree that the other organs and tissues are. The gumma may be infrequent, as it is in all organs, or even rarer, or it may be infrequently diagnosed, both in life and at the autopsy. What this research does show are the facts that the essential lesions of syphilis in the lungs are the same as elsewhere; and, what is extremely important to the clinician, that the lungs of the syphilitic are not normal organs. Our 152 cases of syphilis show the following conditions:

1. Chronic Passive Congestion (Well-marked fibrosis)	124	cases
2. Marked Brown Induration	43	“
3. Marked Fibrosis Without Brown Induration	18	“
4. Hemorrhagic Infarctions	28	“
5. Pulmonary Thrombosis	14	“
6. Edema of the Lungs	35	“
7. Atelectasis (Subpleural)	16	“
8. Bronchopneumonia	45	“
9. Tubercles (Of Clinical Importance)	21	“
10. Excessive Anthracosis	61	“
11. Emphysema	42	“
12. Chronic Pleuritis	19	“
13. Bronchiectasis	6	“
14. Presence of Corpora Amylacea	6	“
15. Pulmonary Gangrene	6	“
16. Fibrosis of Peribronchial Nodes	2	“

A terminal bronchopneumonia or croupous pneumonia occurred in a very high per cent of the cases in connection with an inadequate heart. It is, of course, impossible to state how much of the pulmonary pathology so strikingly shown in this series of cases is due primarily to syphilis of the lung tissue, or secondarily to the effects of syphilis upon the myocardium. A vicious circle will sooner or later be produced, as far as the lungs are concerned. To any primary damage produced in these organs, there will sooner or later be added a chronic passive congestion due to the myocardial lesions. To what extent does this modify the syphilitic process? We can not say now. At any rate the great majority of autopsy cases of syphilis show lungs having a greater or less degree of fibrosis, as do the other organs and tissues, and with this fibrosis they present a varied pathologic picture.

CONCLUSION

The diagnosis of pulmonary syphilis must be made microscopically. The lungs of syphilitics show an incidence of fibrosis comparable with that observed in other organs of the same cases. They show also a high percentage of pulmonary pathologic conditions, in part, at least, referable to the coincident myocardial affection. A certain number of cases (here 12 out of 152) present a specific syphilitic pathology of clinical importance, in the form of gumma, fibrosis, peribronchitis and arteritis. To what extent the high incidence of fibrosis of the lungs is due to syphilis alone can not be decided now, but it is probable that the lung is not exempt from involvement in the mild inflammatory process caused by syphilis in other organs, and which lead eventually to fibrosis.

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A MORE RAPID AND IMPROVED METHOD OF DEMONSTRATING SPIROCHETES IN TISSUES*

(Warthin and Starry's Cover-glass Method)†

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THE best method yet devised for the demonstration of the *Spirochete pallida* in tissues has unquestionably been that of Levaditi, particularly, in our experience, Warthin's modification of this method (*Bulletin No.* 6 *of the International Association of Medical Museums*). Levaditi's original method requires at the very least seven days, usually ten days. Warthin's modification requires about fourteen days. Levaditi's method treats the tissue *en masse.* Aside from the length of time required, the staining in tissue-mass constitutes a very great disadvantage. It is impossible to locate active syphilitic infiltrations and then apply spirochete staining by this method; consequently the search for the spirochete often becomes a needle-in-the-hay-stack affair, with hundreds or thousands of sections to be examined, too often fruitlessly. It has been necessary to take neighboring blocks, one for the spirochete method, the other for ordinary stains, in the attempt to check up the relationship of the spirochete to the tissue lesions. In practical diagnostic work this disadvantage has been a serious handicap. When active syphilitic lesions, or suspected syphilitic areas, have been found in sections taken from a paraffin block and stained with hematoxylin and eosin, it has hitherto been impossible to apply successfully any of the spirochete methods to other sections taken from the block in the attempt to determine the association of spirochetes to such lesions. The only recourse has been to take the paraffin out of the block, run the tissue back through xylol,

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(*This research has been carried out under a grant made by the Interdepartmental Social Hygiene Board, Washington, D. C.)

†From the Pathological Laboratory of the University of Michigan, Ann Arbor.

alcohol and water, and then to carry it through the full Levaditi method. This we have accomplished successfully in some cases; but in others failure results. Moreover, even in expert hands the staining *en masse* gives varying and capricious results, with a too-high proportion of failures. Some laboratory workers are unable ever to obtain satisfactory results with the Levaditi method; and there can be no doubt the time required for the Levaditi method and the difficulties attending it have been so discouraging to the average technician that very few diagnostic pathologic laboratories are making any effort to use the demonstration of spirochetes in tissue as the diagnostic aid it should be. The method is said to be too capricious, too difficult and too time-consuming; therefore it is not used.

What is sorely needed is a method of demonstrating spirochetes in tissue *in sections stained singly*, taken from tissue-blocks so treated that all ordinary stains may be used if desired. This would permit the application of the spirochete method to localized lesions discovered in the routine staining methods. The time must be greatly shortened, ordinary fixations made applicable if possible, and the elements of capricious results avoided. We have for some time been carrying on systematic investigations in the search for a method of this kind, under a grant given this laboratory for this purpose, by the Interdepartmental Social Hygiene Board. In this work we have already hit upon several new methods of importance; and while continuing our researches for still more ideal methods, we are presenting here a method of demonstrating spirochetes in sections mounted on cover-glasses, that in our experience is far better than the old Levaditi method. It has the following advantages.

1. Ordinary formol fixations will give good results. Alcohol fixations also succeed.
2. The sections can be stained singly, on cover-glasses.
3. Time is much shortened; three days are sufficient.
4. Results are more certain than with the Levaditi.

The outline of the method is as follows:

(Warthin and Starry's Cover-glass Method for Demonstrating Spirochete pallida in Sections)

1. Tissue fixed in neutral formol (4 per cent) or alcohol for one to three days. Ordinary routine formol solution will do.

2. Wash thoroughly in distilled water to remove all traces of formol.

3. Imbed in paraffin (alcohol, xylol, paraffin).

4. Cut and mount sections on cover-glasses with albumin fixative.

5. Remove paraffin (xylol, alcohol, water).

6. Place cover-glasses in a saturated solution of ferric alum, or a 4 per cent solution of ferrous ammonium sulphate. Keep in incubator one to two hours.

7. Wash in distilled water.

8. Rinse cover-glass and section in a 2 per cent silver nitrate solution. Cover section with another perfectly clean cover-glass which has also been rinsed in the silver solution. The cover-glasses will be held together by capillary attraction. Place them carefully on the bottom of a bottle of silver nitrate solution. Bottle should be covered with black paper. Cork tightly, and place in incubator for three to twenty-four hours.

9. After impregnation pour off the silver nitrate solution, and rinse in distilled water without removing cover-glasses from bottle. Pour water into bottle, shake gently a few times and then pour off.

10. Pour reducing substance (pyrogallic acid, 4 grams, 40 per cent formol, 5 c.c., distilled water, 100 c.c.) into bottle. See that fluid passes between cover-glasses, by pressing upon cover-glass with glass rod, or by shaking. Reduction must occur uniformly over the section or brown lines will result. Reduction is usually instantaneous. Remove section after two to three minutes, wipe off any brown or black precipitate on the albumin fixative about the section with a cloth, taking care not to touch the section.

11. Wash in distilled water.

12. Absolute alcohol, xylol, balsam.

GENERAL CONSIDERATIONS

Best results are obtained when the fresh tissue is cut about 5 mm. thick before fixing. Four per cent neutral formol is perhaps the best fixing fluid. All formol must be washed out, for it is a reducing agent and if present will interfere with the silver impregnation. After thorough washing the blocks go into 96 per cent alcohol, in which they may be kept for any desired length of time, or the tissue may be run as usual into absolute alcohol, xylol, and imbedded in paraffin.

Sections of the paraffin blocks should not be thicker than 5 microns. Great care should be taken in mounting the sections on the cover-glasses. Three-quarter inch, No. 1 or thin No. 2 covers should be used. A small drop of albumin fixative is placed on the clean cover-glass and thoroughly rubbed over the surface, removing excess by repeatedly rubbing the ball of the finger over the cover-glass and each time wiping off the finger on a clean cloth. By repeatedly rubbing the cover-glass with the dry finger in this way a minimum of albumin fixative is left on the cover-glass, so that there is not a sufficient amount of it to interfere with the silver impregnation. If too much albumin fixative is left on the cover it becomes stained. The properly smeared cover-glasses are placed on clean cardboard, covered with clean paper and kept in the incubator for twelve hours before they are used. They should not be dried over a flame, as this usually results in scorching or incomplete drying, so that the sections float off later.

The sections should not be thicker than 5 microns, preferably 2-3 microns. As they are cut they are floated on warm water that has recently been boiled to prevent bubbles forming on the under side of the section. As the sections flatten out they are caught up on the prepared cover-glasses, the water blotted off, and the cover-glass warmed over the flame until the paraffin begins to melt. They are then placed in the drying oven for two hours, when they are ready to stain.

The staining process should be carried out, as far as possible, in the dark. Brown bottles with wide mouths should be used. These should be covered with black paper, and should have tightly fitting corks.

Remove the paraffin from the sections on the cover-glasses by means of xylol. Remove xylol with absolute alcohol. Then wash cover-glass preparations thoroughly with distilled water to remove all traces of alcohol. Then transfer cover-glasses to a saturated solution of ferric alum or a 4 per cent ferrous ammonium sulphate for one to two hours in the oven, covering staining dish to prevent evaporation and precipitation of dust on the sections. Wash thoroughly in distilled water. (The treatment with iron salts can be given the

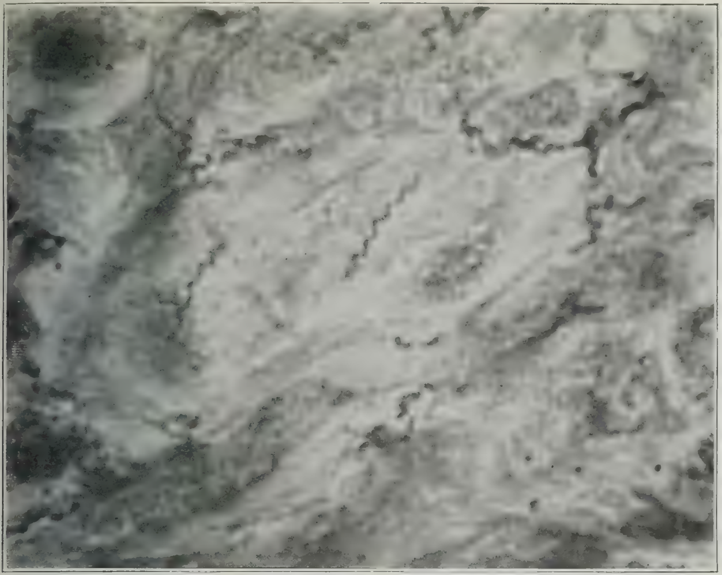

Fig. 1.—Photomicrograph of Spirochete pallida in section from hard chancre, made from ordinary diagnostic block after sections had been examined in hematoxylin and eosin. Tissue had been sent to laboratory rolled up in gauze moistened with formalin. Spirochete stain obtained twelve hours after histologic examination.

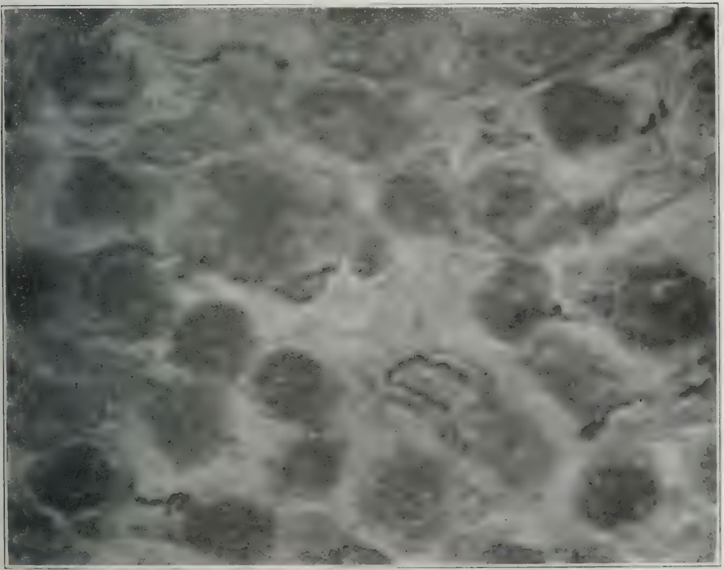

Fig. 2.—Spirochete pallida in syphilitic tonsil. Tonsil had been given routine fixation in 4 per cent formaldehyde solution. Sections stained with hematoxylin and eosin showed the histologic changes regarded by Warthin as syphilitic. This photomicrograph was made from a section obtained from the same paraffin block, stained by the new method within twelve hours.

block of tissue before imbedding, in the oven eight to twenty-four hours, according to the size of the blocks.)

After washing, the cover-glasses are put into the silver nitrate solution in the bottles. A 2 per cent solution of silver nitrate is used; it should be made fresh each time, as stock solutions do not give good results. Ten to 20 c.c. of the solution is sufficient for each bottle. Rinse the cover-glass with the silver solution, place on it another clean cover-glass rinsed in the same silver solution. They are held by capillary attraction, and are then placed carefully on the bottom of the bottle, which is tightly corked, and then placed in the oven, twelve to twenty four hours giving the best results, although fair stains may be obtained at three hours. After impregnation the silver nitrate is poured off, and the cover-glasses rinsed in the bottle with distilled water. The cover-glasses need not be removed from the bottle. The water can be poured into the bottle, which is shaken a few times to insure thorough washing. The water is then poured off, and the reducing substance poured in.

Pyrogallic acid, in the same solution as used for the Levaditi method, makes a good reducing substance.

Pyrogallic acid	4 g.
40 per cent formol	5 c.c.
Distilled water	100 c.c.

A gallic acid solution may also be used. To a 2 per cent gallic acid solution add, drop by drop, a 1 per cent $NaCO_3$ solution, until a drop of the mixture added to a silver nitrate solution causes instant reduction.

The reducing fluid must pass quickly between the cover-glasses. This can be accomplished by applying pressure to the upper cover-glass at the bottom of the bottle or by gently shaking the bottle. If the reducing substance does not pass over the section at an even rate brown lines will be produced wherever the flow stops from the too great reduction of silver nitrate at this point. The reduction should be instantaneous over the whole surface of the section, but it is best to leave the cover-glasses in the reducing fluid for two to three minutes. There may be a brown or black precipitate on the albumin fixative about the section; this should be rubbed off with a clean cloth, care being taken not to touch the section with the cloth. The reduced section should have a faint, dull brownish yellow color. A bright yellow color indicates poor staining of the organisms. As soon as the cover-glass is cleaned the preparation is washed in distilled water, dehydrated in absolute alcohol, cleaned in xylol and mounted in balsam.

The trick of this method is the application of the silver nitrate solution and the reducing substance in *small mass action* between the cover-glasses. The uncovered section can not be successfully treated with silver and reducing solutions, it becomes too black and the precipitate covers up everything. If the cover-glasses become separated in the silver solution during impregnation the section will become covered with a black precipitate. By this capillary attraction method of treatment a minimum amount of silver and reducing substance is admitted so that the spirochetes become more heavily impregnated than the tissue, and are easily seen. They have a deep reddish brown color contrasting sufficiently strongly with the yellow background, as is clearly shown by the two photomicrographs, the sections of which were taken from ordinary tissue blocks in the routine laboratory diagnostic service. The histologic lesions of these, one a chancre, the other a tonsil lesion, were first recognized in the hematoxylin and eosin stains. Taken from routine diagnostic material, these tissues were poorly fixed rather than well fixed. The chancre had been sent to the laboratory by mail; it had been wrapped in formol-soaked gauze, at least two days before arrival, and was then accorded ordinary routine rapid fixation. After the recognition of the histologic lesions it took but twelve hours to demonstrate the spirochetes. As far as time and technical considerations are concerned this is, therefore, a very great improvement over the Levaditi method. Moreover, control series with this method and with the Levaditi, show a much greater element of certainty with the cover-glass preparations. It is much less capricious. The method is not difficult, if directions are intelligently followed. Untrained laboratory workers and students have had no trouble in getting well-stained spirochetes the first time. Results will vary, probably due to slight differences in physical conditions and in washing. More silver nitrate may be washed out between the cover-glasses in one case than in another. If the section turns out a bright yellow the spirochetes are usually not well stained or do not show at all. When the section has a dull, faint color the indications are for well-stained spirochetes if they are present. Ordinarily the reticulum stains as the other tissue elements, but even when of a deeper brown tone it does not interfere with the search for the spirochetes. The use of the iron salts seems to inhibit staining of the tissue, and brings out the organisms more clearly. By treating the tissue with iron salts the organisms can be stained in tissues fixed routinely with formol or alcohol; and it becomes possible to demonstrate them when the Levaditi method fails. The chief differences in appearance between the cover-glass preparations and the Levaditi ones, are the dark reddish brown color of the spirochetes, the less deeply stained tissue and less abundant precipitate of the former. The spirochetes are never as black as with the Levaditi, but the photomicrographs (taken with a color screen) are as good as those obtained by the latter method.

The successful operation of this new method consists in a trick of producing certain physical conditions between two cover-glasses, with a minimal amount of reaction between the tissue and the silver and reducing solutions, so that the spirochetes are more deeply stained than the tissue-elements, and precipitates are avoided. The use of iron salts favors the differential staining of tissue and spirochetes. When the knack of using this method is acquired, and it is very easily acquired, sections from routine diagnostic blocks can be used, much time can be saved, and results seem more certain. It is, then, a great improvement over the old Levaditi method or any of its modifications. We do not, however, believe, that we have yet found the ideal method for which we are searching, and our investigation will continue in the hope of achieving it.

SECOND IMPROVED METHOD FOR THE DEMONSTRATION OF SPIROCHAETA PALLIDA IN THE TISSUES

WARTHIN AND STARRY'S SILVER-AGAR COVER-GLASS METHOD *

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AND
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In January, 1920, we described[1] our first improved and more rapid method for the demonstration of *Spirochaeta pallida* in tissue sections, formaldehyd-fixed, embedded in paraffin, and mounted on cover-glasses. The essential features of this method consist in the application of the silver nitrate solution and the reducing substance in small mass action between cover-glasses, so that a minimum amount of silver and reducing substance are admitted through capillary attraction to the section. When this is managed as directed in the method, the spirochetes become more heavily impregnated than the tissue elements, standing out in sufficient contrast to the latter, without the formation of a concealing precipitate. We found this to be the first practical method of applying silver impregnation to spirochetes in single sections, and a decided improvement over the Levaditi method of impregnation in bulk. One of the chief advantages gained was the great saving in time—from ten to fourteen days to twelve hours for the new method. By it also sections from ordinary diagnostic blocks, fixed in formaldehyd, can be used whenever the histologic findings suggest the occurrence of spirochetal infection. We have found the method more certain and less capricious than the old Levaditi method or any of its modifications. Since publishing a description of it we have had corroboration of these points from a number of other laboratory workers.

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* This research has been carried out under a grant made by the Interdepartmental Social Hygiene Board, Washington, D. C.

* From the Pathological Laboratory of the University of Michigan Medical School.

[1] Warthin, A. S., and Starry, A. C.: Rapid and Improved Method of Demonstrating Spirochetes in Tissues (Warthin and Starry's Cover-Glass Method), Am. J. Syph. 4: 97 (Jan.) 1920.

[1] Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.

We are now presenting a method which we consider as great an improvement on the former, as that was on the older methods, in that it possesses these advantages:

1. The time is much shortened; the entire procedure may be carried out in less than one hour after the sections have been mounted on cover-glasses.

2. The results are more certain. We have demonstrated spirochetes in tissues by this method when all others have given negative results.

3. It is more simple, and more easily carried out.

WARTHIN AND STARRY'S SILVER-AGAR METHOD

1. Tissues fixed in neutral formaldehyd.
2. Embed in paraffin.
3. Cut, and mount sections on cover-glasses with albumin fixative.
4. Remove paraffin (xylene, alcohol, water).
5. Rinse cover-glass with section in 2 per cent. silver nitrate; cover wet section with another perfectly clean cover-glass, so that they are held together by capillary attraction; then place them carefully in a bottle of 2 per cent. silver nitrate and place in incubator for from thirty minutes to one hour; then remove from the silver nitrate and separate cover-glasses.
6. Place cover-glass with section in this reducing mixture:

	C.c.
Two per cent. silver nitrate solution	3
Warm glycerin	5
Warm 10 per cent. aqueous gelatin solution	5
Warm 1.5 per cent. agar suspension	5
Five per cent. aqueous hydroquinone solution	2

7. After the section is reduced, remove and rinse in 5 per cent. sodium thiosulphate (hyposulphite) solution.
8. Rinse in distilled water.
9. Absolute alcohol, xylene, balsam.

GENERAL CONSIDERATIONS

Fixation should be complete to give the best results. Thin slices of tissue, from 5 to 7 mm. thick, left in 4 per cent. neutral formaldehyd (10 per cent. formaldehyd solution) from one to three days give the best results. If tissue is put into alcohol before the formaldehyd fixation is complete, the results are less satisfactory. If the formaldehyd fixation is complete it is not necessary to wash the tissue in water before putting it into 96 per cent. alcohol. Some of our best results have been obtained in tissues kept many years in 4 per cent. formaldehyd. The importance of fixing tissues as soon as removed from the body, or as soon as possible after death, must be emphasized again.

From 96 per cent. alcohol the tissue is run through absolute alcohol, two changes of xylene and two of 52 C. paraffin. The sections should be cut about 5

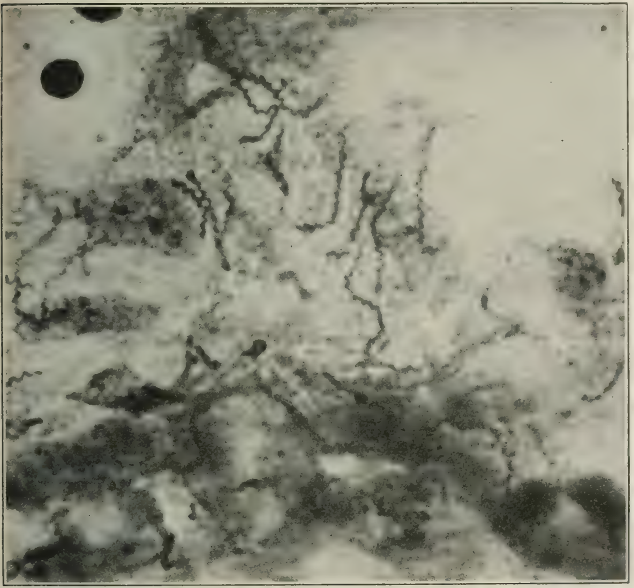

Fig. 1.—Spirochaeta pallida in kidney of a congenital syphilitic. The spirochetes are in small, localized, inflammatory areas between the tubules and around the blood vessels. Tissue fixed in formaldehyd, blocked in paraffin; stain obtained by silver-agar method within one hour after cutting sections. Photographed with a Zeiss 2 mm. oil-immersion, compensating ocular No. 4, with a bellows length of 85 cm.

microns thick for the best results, although from 8 they are floated on warm distilled water which has recently been boiled to drive off the air. The under or shiny side of the section is placed on the water. to 12 microns give practical sections. As they are cut When the sections have flattened out on the warm water they are caught up on the prepared cover-glasses, the water blotted off, and then dried over the flame

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[1] **Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.**

or in the drying oven. The cover-glasses should be No. 1 or thin No. 2, three-quarter inch squares, or larger if the size of the section requires. They must be perfectly clean, free of all dirt and grease. A *minimum* amount of albumin fixative should be spread evenly on the clean cover-glass, so that there will not be enough of it to become heavily stained. The prepared cover-glasses should be placed on a clean card-board, covered with clean paper and dried in the incubator for twelve hours before using. They should not be dried by passing through the flame. It is advisable, therefore, to keep a supply of such prepared cover-glasses on hand.

After the mounted paraffin sections have been dried on the cover-glasses, the paraffin is removed by heating over the flame and dropping into xylene, followed by absolute alcohol and then distilled water.

The silver impregnation should be carried out in the dark (dark bottles covered with black paper). Wide-mouthed bottles with tightly fitting corks should be used. The mounted cover-glass is taken from the distilled water, rinsed in 2 per cent. silver nitrate solution, and then covered with another clean cover-glass also wet with the silver solution. The silver solution should always be freshly made, and should never be used after it is from 3 to 4 days old. During this time the same solution may be used over and over again, if kept uncontaminated and in the dark bottle. The bottle should contain enough of the silver solution so that when the cover-glasses are placed on edge against the side of the bottle, it will not completely cover them. The cover-glasses are held together by capillary attraction, and if placed against the side of the bottle wet and the silver solution then poured in so as not to cover them completely, they will be held upright also by capillary attraction, and will not slip apart. The bottle is then tightly corked and placed in the incubator for from thirty minutes to one hour. After impregnation, the cover-glasses are removed, separated, and the mounted section put into the reducing mixture section side up.

The reducing mixture consists of 3 c.c. of a 2 per cent. silver nitrate solution, 5 c.c., of warm glycerin, 5 c.c. of a warm 10 per cent. gelatin solution, and 5 c.c. of a 1.5 per cent. warm agar suspension, to which mixture from 0.25 to 2 c.c. of a 5 per cent. hydroquinone solution is added just before using. The warm glycerin and gelatin solutions and the silver nitrate are first thoroughly mixed, then the agar suspension is stirred in with a glass rod, and finally the hydroquinone, just before the sections are placed in the mixture. The agar suspension must be carefully made. One and five-tenths gm. of agar cut up into small bits is added to 100 c.c. of distilled water and carefully and slowly heated to the boiling point, being constantly stirred with a glass rod. When the agar has gone into fine suspension, the solution is poured into a bottle, which is corked lightly and kept on top the paraffin oven. Should the agar become flaky and settle out, it must be brought to the boiling point again with constant stirring. It should be just thin enough to pour, and not too thin and watery. The glycerin and gelatin solutions can also be kept warm on top the paraffin oven.

The amount of hydroquinone added to the reducing mixture varies somewhat with the tissue and the fixation. In general it is best to use as small an amount as possible so that the reduction is not too rapid. A slow reduction usually gives the best results; but if too slow, precipitates will form and the spirochetes will not be well stained. Usually from 0.5 to 1 c.c. gives the best results; but in some cases more may be required. After the hydroquinone has been added, the mixture is stirred vigorously for a short time. It is then poured into a staining dish, and the mounted section removed from the silver solution, the coverglasses separated, and that holding the section immersed in the reducing mixture for a number of seconds until reduction is complete. The longer the section is in the reducing mixture, the darker it will be. When it becomes a light reddish brown it is removed and washed in a 5 per cent. sodium thiosulphate solution, then rinsed in distilled water, dehydrated in absolute alcohol, cleared in pure xylene, and mounted in balsam. When the sections have been properly stained they will now be light reddish brown. If a deep brown or black, the tissue will be too deeply stained and the

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[1] **Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.**

spirochetes not sufficiently contrasted. Usually the albumin fixative on the cover-glass about the section is stained somewhat, and this can be rubbed off with a clean cloth, care being taken not to touch the section with the cloth. The upper surface of the cover-glass should be similarly cleaned. The section, of course, must never be allowed to get dry after the paraffin has been removed.

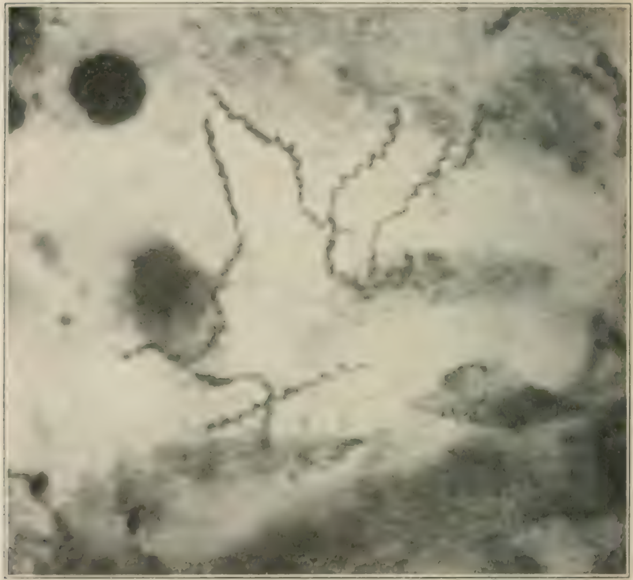

Fig. 2.—Spirochaeta pallida in kidney of a congenital syphilitic. The spirochetes are in small, localized, inflammatory areas between the tubules and around the blood vessels. Tissue fixed in formaldehyd, blocked in paraffin, stain obtained by silver-agar method within one hour after cutting sections. Photographed with a Zeiss 2 mm., oil immersion, compensating ocular No. 4, with a bellows length of 155 cm.

The use of the second cover-glass during the impregnation in the silver solution seems to be an essential feature of the method. We have never been able to secure good results by leaving the sections uncovered during impregnation. The spirochetes will stain only very faintly or not at all; precipitates more readily occur, and the tissue elements are more deeply stained.

It is important that the alcohol used be pure, and contain no mercuric chlorid, copper or other metal. Alcohol dehydrated over copper sulphate should not be used. The tissues are easily mordanted, and the differentiation of the spirochete made difficult or impossible.

All solutions should be made in distilled water; and all glass-ware must be clean. Acid fumes should be avoided.

Our experience has taught us that not all formaldehyd-fixed tissues react to the silver impregnation method in the same way. Controls show that, with the same solutions and same conditions otherwise, some tissues appear granular, some a bright yellow, and others brown or black, while others will not stain at all. We believe that these differences in staining reactions are in part due to slight differences in fixation, contamination of the formaldehyd, etc., giving rise to differences in the process of reduction. We have found that by changing the reaction of the tissue before staining, it is often possible in such cases to affect the tissue conditions to such an extent that good staining results can be obtained. The best results have been obtained by the use of a 1 per cent. solution of uranium or copper nitrate, or a 0.5 per cent. solution of ferric alum. This is accomplished by placing the sections, from water, after the removal of the paraffin, in one of these solutions for several minutes, and then washing thoroughly in distilled water before putting them into the silver solution. These solutions do not act uniformly in all cases. Uranium nitrate usually gives the best results, as, after its use, the tissue elements do not stain so deeply, leaving the spirochetes better differentiated. Copper nitrate and ferric alum have given especially good results in isolated cases of poor formaldehyd fixation. If the tissues are well fixed in formaldehyd, it is not necessary to use any one of these reagents, and they should be tried only when the method proper does not yield good results.

Aside from the use of the second cover-glass to cover the section during the impregnation, the successful operation of the method depends on the reduction process. This can be controlled to a great degree by

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[1] Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.

varying the amount of hydroquinone and also by the temperature. After a little experience in judging the color obtained by reduction there should be no trouble in obtaining sufficiently good stains for diagnostic purposes. With a little more skill obtained by practice, the most beautiful preparations can be easily obtained. Any failures or inconstant results are due to differences in the physical conditions of the reducing mixture or in the fixation of the tissue. As mentioned above, changing the reaction of the tissue by means of uranium or copper nitrate, or by ferric alum, will sometimes remedy the difficulty.

We regard this method as by far the best one yet devised for the demonstration of spirochetes in tissues. The organisms are dark reddish brown to jet black against a very light brown. With experience it can be so manipulated that only the spirochetes and the nuclei of the tissue are stained, so that a beautiful contrast for demonstration purposes or photomicrographic work is obtained.

Further, the rapidity of the method as compared to all other methods for spirochetes in tissue, and its applicability to single sections make it the most practical method for diagnostic work yet devised.

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Segundo Método Perfeccionado Para la Demostración del Espiroqueto Pálido en los Tejidos

El Método de Warthin y Starry en Cubreobjetos de Agar Argéntico

POR EL

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Y

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ANN ARBOR, MICH.

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[1] Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.

SEGUNDO METODO PERFECCIONADO PARA LA DEMOSTRACION DEL ESPIROQUETO PALIDO EN LOS TEJIDOS

EL METODO DE WARTHIN Y STARRY EN CUBREOBJETOS DE AGAR ARGENTICO *

POR EL
DR. ALFRED SCOTT WARTHIN, PhD.
Y
ALLEN C. STARRY
ANN ARBOR, MICH.

En Enero, 1920, describimos [1] nuestro primer método perfeccionado y rápido para demostrar el *Spirochaeta pallida* en los cortes fijados en formaldehido, incrustados en parafina y montados en cubreobjetos. Las características de este método consisten en aplicar la solución de nitrato de plata y la substancia reductora en masa pequeña para que obre entre los cubreobjetos, de modo que sólo llegue al corte por medio de la atracción capilar una cantidad mínima de plata y de substancia reductora. Cuando esto se hace del modo indicado en el procedimiento, los espiroquetos se impregnan más que los elementos histológicos, destacándose en contraposición a los últimos, sin que se forme un precipitado que los oculte. Descubrimos que éste era el primer método práctico de aplicar la impregnación argéntica a los espiroquetos en cortes aislados y que constituía un perfeccionamiento marcado sobre el método de Levaditi de impregnación en masa. Uno de sus principales méritos era el gran ahorro de tiempo—de diez a catorce días con el método viejo a doce horas, con el nuevo. Con éste, además, pueden usarse cortes

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* Del Laboratorio Patológico de la Facultad de Medicina de la Universidad de Michigan.

[1] Warthin, A. S., y Starry, A. C.: Rapid and Improved Method of Demonstrating Spirochetes in Tissues (Warthin and Starry's Cover Glass Method), Am. J. Syph. 4: 97 (Eno.) 1920.

[1] Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.

de las masas ordinarias para el diagnostico, fijos en formaldehido, siempre que los hallazgos histológicos indiquen la existencia de infeccion espiroquetica. Hemos descubierto que el método es más seguro y menos caprichoso que el antiguo metodo de Levaditi o cualquiera de sus modificaciones. Después de publicar su descripcion, hemos visto corroborados estos puntos por varios otros investigadores de laboratorio.

Presentamos ahora un metodo que consideramos un perfeccionamiento tan grande sobre el primero, como aquel lo fue sobre los metodos antiguos, por poseer tres ventajas:

1. Se acorta mucho el tiempo; todo el procedimiento puede llevarse a cabo en menos de una hora despues de montarse los cortes en cubreobjetos.

2. Los resultados son más seguros. Hemos demostrado espiroquetos en los tejidos con este método, cuando todos los demás han producido resultados negativos.

3. Es más sencillo y se lleva a cabo con más facilidad.

II. METODO DE AGAR-PLATA DE WARTHIN Y STARRY

1. Fíjense los tejidos en formaldehido neutro.

2. Incrústense en parafina.

3. Secciónense y móntense los cortes en cubreobjetos, con fijador de albúmina.

4. Sepárese la parafina (xilol, alcohol, agua).

5. Enjágüese el cubreobjetos que contiene el corte, en nitrato de plata al 2 por ciento; cúbrase el corte húmedo con otro cubreobjetos perfectamente limpio, de modo que se mantengan juntos por la atracción capilar; luego, colóquense cuidadosamente en un frasco con nitrato de plata al 2 por ciento y colóquense en la incubadora de treinta minutos a una hora; sáquense luego del nitrato de plata y sepárense los cubreobjetos.

6. Póngase el cubreobjetos con el corte en esta mezcla reductora:

	C.c.
Solución de nitrato de plata al 2 por ciento	[illegible]
Glicerina tibia	[illegible]
Solución tibia de gelatina acuosa al 10 por ciento	[illegible]
Suspensión tibia de agar al 1.5 por ciento	[illegible]
Solución al cinco por ciento de hidroquinona acuosa	[illegible]

7. Después de reducirse el corte, sáquese y enjágüese en solución al 5 por ciento de tiosulfato de sodio (hiposulfito).

8. Enjágüese en agua destilada.

9. Alcohol absoluto, xilol, bálsamo.

CONSIDERACIONES GENERALES

Para obtener los mejores resultados, la fijación debe ser absoluta. Los cortes finos de tejido de un espesor de 5 a 7 mm., preservados de uno a tres días en formaldehido neutro al 4 por ciento (solución de formol al 10 por ciento), dan los mejores resultados. Si se coloca el tejido en alcohol antes de que se complete la fijación en formaldehido, los resultados son menos satisfactorios. Si se completa la fijación en formaldehido, no es necesario lavar el tejido en agua antes de ponerlo en alcohol al 96 por ciento. Hemos obtenido

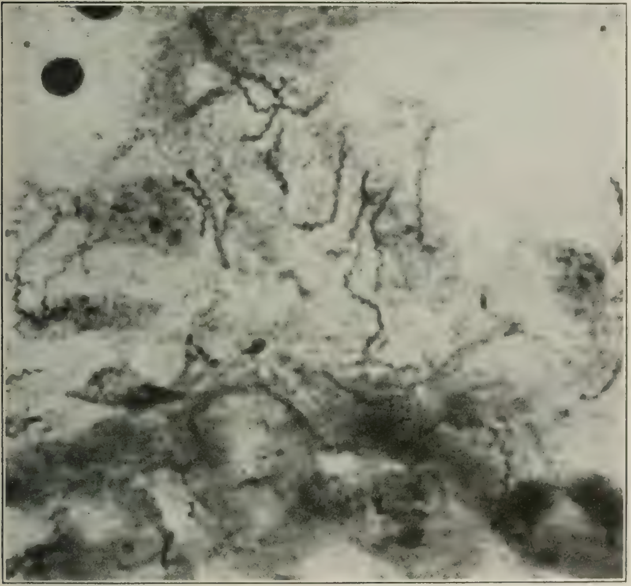

Fig. 1.—El espiroqueto pálido en el riñón de un sifilítico congénito. Los espiroquetos se hallan en las pequeñas áreas inflamatorias, localizadas, entre los túbulos y alrededor de los vasos sanguíneos. El tejido en formaldehido, incrustado en parafina; se coloreó por el método del agar argéntico a la hora de hacer el corte. Fotografiado con un Zeiss de 2 mm. de inmersión en aceite, ocular compensatorio No. 4, con un fuelle de 85 cm. de largo.

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[1] **Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.**

algunos de nuestros mejores resultados con tejidos conservados muchos años en formaldehido al 4 por ciento. Debemos preconizar de nuevo la importancia de fijar los tejidos, apenas se separen del cuerpo o lo más pronto posible después de la muerte.

Después del alcohol al 90 por ciento, se pasa el tejido por alcohol absoluto, dos cambios de xilol y dos de parafina a 52 C. Los cortes deben tener un espesor de 5 micras, aunque los cortes de 8 a 12 micras también son prácticos. A medida que se seccionen, se ponen a flotar en agua destilada tibia que se ha hervido recientemente para expulsar el aire. Se coloca en el agua el lado inferior o brillante del corte. Cuando se han aplastado los cortes en el agua tibia se cogen en los cubreobjetos preparados, se seca el agua con secantes y luego se deshidratan a la lámpara o en la secadora. Los cubreobjetos deben ser No. 1 o No. 2, en cuadrados de tres cuartos de pulgada (2 cm.) o mayores si lo exige el tamaño del corte. Deben hallarse perfectamente limpios y libres de toda suciedad y grasa. Debe extenderse uniformemente sobre el cubreobjetos limpio una cantidad *mínima* de fijador de albúmina, de modo que no sea suficiente para colorarse intensamente. Los cubreobjetos preparados deben colocarse sobre un cartón limpio, cubierto con papel también limpio y secarse en la incubadora doce horas antes de emplearlos. No debe secarse, pasándolos sobre la flama. Por consiguiente, conviene tener a mano una cantidad suficiente de estos cubreobjetos preparados.

Después de secarse los cortes parafinados montados en los cubreobjetos, se quita la parafina, calentándolos a la flama y echándolos en xilol, seguido de alcohol absoluto y luego agua destilada.

La impregnación argéntica debe verificarse a obscuras (frascos opacos cubiertos con papel negro). Deben emplearse bocales con corchos bien ajustados. Se saca el cubreobjetos montado del agua destilada, se enjagüa en solución de nitrato de plata al 2 por ciento y luego se cubre con otro cubreobjetos limpio, también humedecido con la solución argéntica. Debe siempre prepararse la solución argéntica fresca y no emplearse si tiene más de tres o cuatro días. Durante este tiempo, la misma solución puede emplearse vez tras vez, si no se contamina y se guarda en el frasco opaco. El frasco debe contener suficiente solución argéntica, de modo que cuando se coloquen los cubreobjetos de lado contra el lado del frasco, no los cubra del todo. Los cubreobjetos se mantienen juntos por la atracción capilar y si se colocan húmedos contra el lado del frasco y se vierte sobre ellos la solución argéntica de modo que no los cubra del todo, también se mantendrán horizontalmente por la atracción capilar y no se separarán. Luego se tapa herméticamente el frasco y se coloca en la incubadora de treinta minutos a una hora. Después de la impregnación, se sacan los cubreobjetos, y se coloca el corte en la substancia reductora con el lado del corte hacia arriba.

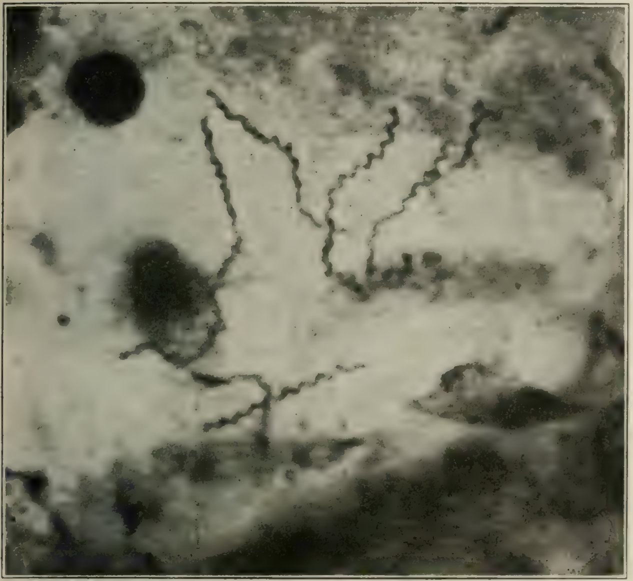

Fig. 2.—El espiroqueto pálido en el riñón de un sifilítico congénito. Los espiroquetos se hallan en las pequeñas áreas inflamatorias, localizadas, entre los túbulos y alrededor de los vasos sangíneos. El tejido fijo en formaldehido, incrustado en fina; se obtuvo el corte por el método del agar argéntico, a la hora de hacer el corte. Fotografiado con un Zweiss de 2 mm. de inmersion en aceite, ocular compensatorio No. 4, con un fuelle de 155 cm. de largo.

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[1] Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.

La mezcla de reduccion consiste en 3 c.c. de una solucion de nitrato de plata al 2 por ciento, 5 c.c. de glicerina tibia, 5 c.c. de una solucion tibia de gelatina al 10 por ciento y 5 c.c. de una suspension tibia de agar al 1.5 por ciento, a lo cual se agregan, precisamente antes de emplearla de 0.25 a 2 c.c. de una solución al 5 por ciento de hidroquinona. Antes que nada se mezclan bien las soluciones tibias de glicerina y de gelatina y el nitrato de plata, luego se vierte la suspensión de agar, agitándose con una varilla de cristal y por fin la hidroquinona precisamente antes de colocarse los cortes en la mezcla. Debe prepararse cuidadosamente la suspensión de agar. A 100 c.c. de agua destilada se agregan 1.5 gm. de agar, cortado en pedacitos muy pequeños, y se calienta cuidadosa y lentamente al punto de ebullición, agitándose constantemente con una varilla de cristal. Cuando el agar se ha convertido en una suspensión muy fina, se vierte la solución en una botella, que se tapa ligeramente y se coloca encima del horno de la parafina. Si el agar se vuelve coposo y se asienta, debe llevarse de nuevo al punto de la ebullición, agitándose constantemente. Debe ser lo suficientemente claro para verterlo, pero no demasiado claro y acuoso. Las soluciones de glicerina y gelatina, pueden también mantenerse tibias encima del horno de parafina.

La cantidad de hidroquinona que se agrega a la mezcla reductora varía algo, según el tejido y la fijación. En general, conviene más emplear la menor cantidad posible, de modo que la reducción no sea demasiado rápida. Por regla general, una reducción lenta da mejores resultados; pero si es demasiado lenta, se formarán precipitados y no se teñirán bien los espiroquetos. Por regla general, de 0.5 a 1 c.c. dan mejores resultados; pero en algunos casos, quizás se necesite más. Después de agregarse la hidroquinona, se agita enérgicamente la mezcla por algún tiempo. Se vierte luego en una placa de coloración y se saca el corte montado de la solución argéntica, se separan los cubreobjetos y el que contiene el corte se sumerge en la substancia reductora por varios segundos, hasta que se complete la reducción. Mientras más tiempo esté el corte en la mezcla reductora, más obscuro se volverá. Cuando toma un color rojo parduzco claro, se saca y se lava en una solución al 5 por ciento de tiosulfato de sodio, luego se enjagüa en agua destilada, se deshidrata en alcohol absoluto, se limpia en xilol puro y se monta en bálsamo. Cuando los cortes se han coloreado debidamente, tienen un color rojo parduzco claro. Si se vuelven de un color pardo obscuro o negro, el tejido se ha teñido demasiado intensamente y los espiroquetos no se destacarán bien. Por lo general, se colorea algo el fijador de albúmina en el cubreobjetos alrededor del corte y esto puede quitarse con un paño limpio, teniéndose cuidado de no tocar el corte. Debe limpiarse del mismo modo la superficie superior del cubreobjetos. Por supuesto, no debe dejarse nunca que el corte se seque, después de quitarse la parafina.

El uso del segundo cubreobjetos durante la impregnación en la solución argéntica, parece constituir una característica indispensable del método. No hemos podido nunca conseguir buenos resultados si no cubrimos los cortes durante la impregnación. Los espiroquetos se colorearán sólo muy débilmente o nada en absoluto; ocurren más fácilmente precipitados y los elementos histológicos se tiñen más intensamente.

Es importante que el alcohol sea puro y que no contenga cloruro mercúrico, cobre ni ningún otro metal. No debe emplearse alcohol deshidratado sobre sulfato de cobre. Los tejidos ceden con facilidad a la acción el mordiente y se vuelve difícil o imposible diferenciar los espiroquetos.

Todas las soluciones deben hacerse en agua destilada y la cristalería debe ser limpia. Deben evitarse los vapores ácidos.

Nuestra experiencia nos ha demostrado que no todos los tejidos fijos en formaldehido reaccionan a la impregnación argéntica del mismo modo. Los testigos indican que con las mismas soluciones y los mismos métodos generalmente, algunos tejidos toman forma granular, otros toman un color amarillo brillante y otros pardo o negro, en tanto que otros no se colorean absolutamente. Creemos que estas diferencias en las reacciones de coloración se deben en parte a diferencias ligeras en la fijación, la contaminación del formaldehido, etc., que causan diferencias en el proceso de reducción. Hemos descubierto que cambiando la reacción del tejido antes de colorearlo, a menudo es posible afectar las condiciones histológicas a tal punto que pueden obtenerse buenos resultados de coloración. Hemos obtenido los resultados mejores con una solución al 1 por ciento de nitrato de uranio o de cobre o una solución al 0.5 por ciento de alumbre férrico. Esto se logra

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[1] **Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.**

colocando los cortes del agua, después de quitar la parafina, en una de estas soluciones por varios minutos y lavándolos luego perfectamente en agua destilada, antes de colocarlos en la solución de plata. Estas soluciones no obran uniformemente en todos los casos. El nitrato de uranio por lo general es el que da mejores resultados, puesto que, después de usarlo, los elementos histológicos no se tiñen tan intensamente, lo cual permite diferenciar mejor los espiroquetos. El nitrato de cobre y el alumbre férrico han dado buenos resultados, en particular en casos aislados de mala fijación en formaldehido. Si se han fijado bien los tejidos en formaldehido, no es necesario emplear ninguno de estos reactivos y deben probarse, únicamente cuando el método de por sí no produce buenos resultados.

Aparte del empleo del segundo cubreobjetos para cubrir el corte durante la impregnación, el éxito del método depende del proceso de reducción. Esto puede dominarse en gran parte variando la cantidad de hidroquinona y también por la temperatura. Después de alguna experiencia, juzgando por la coloración obtenida por la reacción, no debe haber dificultad alguna en obtener colorantes suficientemente buenos para fines diagnósticos. Con alguna destreza, debida a la práctica, pueden obtenerse con facilidad preparados muy hermosos. Todo frasco o resultados inconstantes se deben a las diferencias en las condiciones físicas de la substancia reductora o en la fijación de los tejidos. Como hemos dicho, el cambiar la reacción histológica por medio de nitrato de uranio o de cobre o de alumbre férrico, a veces evitará la dificultad.

Consideramos este método muy superior a todos los propuestos hasta la fecha para la demostración de los espiroquetos en los tejidos. Los microbios se presentan en color rojo parduzco obscuro, a negro de azabache, contra un fondo pardo muy claro. A medida que se obtiene experiencia, puede uno arreglárselas de modo que sólo se coloreen los espiroquetos y los núcleos del tejido, de modo que se obtienen un contraste bello para fines de demostración y fotomicrografía.

Además, la rapidez del método, comparado con todos los otros métodos para teñir los espiroquetos en los tejidos y su aplicabilidad a cortes aislados, lo convierten en el método más práctico para el diagnóstico, que se ha inventado hasta la fecha.

[1] Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.

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38 (1620)

Improved methods for staining spirochaeta pallida in tissue.[1]

By **Aldred S. Warthin** and **Allen C. Starry.**

[*Ann Arbor, Michigan.*]

The two methods outlined here present the first satisfactory ones devised for the staining of spirochetes in single sections of tissue mounted upon cover-glasses. We consider them of great value for the following reasons: They are more certain than the Levaditi method of staining in bulk; the time required is shortened to hours, instead of the days required by that method; they have a much greater applicability to practical diagnostic work in that they can be used for single sections, thus permitting a closer control of histological findings.

I. Warthin and Starry's Cover-glass Method.

1. Fix tissues in 4 per cent. formol.
2. Wash thoroughly in distilled water.
3. Imbed in paraffin (alcohol, xylol, paraffin).
4. Cut; mount sections on cover-glasses with albumin fixative.
5. Remove paraffin from section (xylol, alcohol, water).
6. Place cover-glass in a saturated solution of ferric alum, or a 4 per cent. solution of ferrous ammonium sulphate, in incubator for 1 to 2 hours.
7. Wash in distilled water.
8. Rinse cover-glass with section in a 2 per cent. silver nitrate solution. Cover section with another perfectly clean cover-glass which has also been rinsed in the silver solution, so that the cover-glasses are held together by capillary attraction. Then place them carefully on the bottom of a wide-mouthed dark bottle covered with black paper, and cover them with the silver nitrate solution. Cork tightly, and put into incubator for 3 to 24 hours.

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[1] Researches conducted under a grant from the Interdepartmental Social Hygiene Board, Washington.

9. After impregnation pour off the silver nitrate solution and rinse in distilled water without removing cover-glasses from bottle, by pouring the water into the bottle, shaking gently, and then pouring off.

10. Pour reducing fluid (pyrogallic acid, 4 grams; 40 per cent. formol, 5 cc.; distilled water, 100 cc.) into the bottle. See that fluid passes between cover-glasses by pressing upon them with a glass rod, or by shaking. Reduction is almost instantaneous; it should occur evenly over the section or brown lines will result. After 2 to 3 minutes remove cover-glasses, separate, wipe off with a cloth any precipitate on the albumin fixative about the section, taking care not to touch the latter.

11. Wash in distilled water.

12. Dehydrate in absolute alcohol, clear in xylol, then balsam.

The reduced section should have a faint, dull brownish-yellow color. If the color is bright yellow the organisms will be poorly stained. The spirochetes should have a deep reddish brown color contrasting sufficiently well with the background, if the procedure has been successful.

2. WARTHIN AND STARRY'S SILVER-AGAR COVER-GLASS METHOD.

1. Fix tissue in 4 per cent. neutral formol.
2. Imbed in paraffin (absolute alcohol, xylol, paraffin).
3. Cut, mount sections on cover-glasses with albumin fixative.
4. Remove paraffin (xylol, alcohol, water).
5. Rinse cover-glass with section in 2 per cent. silver nitrate; cover wet section with another perfectly clean cover-glass, so that they are held together by capillary attraction; then place them carefully in a bottle of 2 per cent. silver nitrate, and place in incubator for 30 to 60 minutes; then remove the silver nitrate and separate cover-glasses. They must not separate while in the solution.
6. Place cover-glass with section in the following reducing mixture:

2 per cent. silver nitrate solution	3 cc.
Warm glycerin	5 cc.
Warm 10 per cent. aqueous gelatin	5 cc.
Warm 1½ per cent. agar suspension	5 cc.
1 per cent. aqueous hydroquinone solution	2 cc.

7. Reduce until section is a light reddish brown (several seconds); remove and rinse in 5 per cent. sodium hyposulphite solution.

8. Rinse in distilled water. Clean off with a cloth any precipitate on the cover-glass.

9. Absolute alcohol-xylol-balsam.

The mounted section should have a light reddish brown color; if too deep brown or black the spirochetes will not be sufficiently contrasted. They should appear dark reddish brown to jet black against a very light brown background.

In some cases of poor fixation of the tissue with poor staining of the spirochetes we have found that if the sections before being put into the silver solution are treated for several minutes in a 1 per cent. solution of uranium or copper nitrate, or a 0.5 per cent. solution of ferric alum, the tissue-reaction is changed in some way so that good staining results. These solutions do not act uniformly in all cases. After their use the section must be thoroughly washed in distilled water before it is put into the silver nitrate solution.

A CASE OF AYERZA'S DISEASE:

CHRONIC CYANOSIS, DYSPNEA, AND ERYTHREMIA, ASSOCIATED WITH SYPHILITIC ARTERIOSCLEROSIS OF THE PULMONARY ARTERIES

BY

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A CASE OF AYERZA'S DISEASE:

CHRONIC CYANOSIS, DYSPNEA, AND ERYTHREMIA, ASSOCIATED WITH SYPHILITIC ARTERIOSCLEROSIS OF THE PULMONARY ARTERIES

By Aldred Scott Warthin, Ph.D., M.D.,
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THE discovery by Vaquez, in 1892, of the syndrome of chronic cyanosis, persistent polycythemia, and enlargement of liver and spleen, in the absence of organic heart involvement, and Osler's service later in calling the attention of the medical profession to this new complex, established a definite place for it in nosology as Vaquez's disease, Osler's disease, Osler-Vaquez disease, erythremia, primary polycythemia, splenomegalic polycythemia, polycythemia with chronic cyanosis, myelopathic polycythemia, cryptogenic polycythemia, erythrocytosis megalosplenica, etc. Lucas (1) collected 149 undoubted and 30 questionable cases from the literature. Since his paper the number reported has increased to over 200. Lucas, in his summary, came to the conclusion that, in the light of the present knowledge of the disease, it was difficult to establish a hard-and-fast line between cases of polycythemia, probably secondary in form but of obscure origin, on the one hand, and unquestionable cases of primary polycythemia or erythremia on the other. The 23 reported autopsies had thrown but little light on this question.

Since Lucas' paper the question as to the primary or secondary nature of the Osler-Vaquez syndrome has received more attention, and there is an increasing number of cases in which the syndrome has been found associated with other conditions in such a way as to make it certain that the symptom-complex was purely secondary. The separation of a primary polycythemia from a secondary erythrocytosis has become more difficult, and the question may well be asked if a primary Osler-Vaquez disease exists. The uncertainty attending this question has led recent writers to split up the Osler-Vaquez disease into a number of groups. The fact that cases are reported under such titles, or are classed as "Polycythemia without splenomegaly," "Polycythemia without cyanosis," the "frustrate form," congenital form, cardiac form, "Geisbock's disease," "Blumenthal's disease," etc., reveals the confusion attending the effort to fix the symptom-complex as a distinct morbid entity. Similarly the attempts to separate forms upon a basis of the number of red cells, state of the bone-marrow, etc., are evidence of the difficulty in giving the syndrome a fixed position in nosology.

Does a primary erythremia exist? The writer believes not, certainly not in cases showing chronic cyanosis and dyspnea. Why should a case of pure or absolute polyglobulism have either cyanosis or dyspnea? On the other hand, there is every reason why a case of chronic ceyanosis and dyspnea should develop a chronic erythremia. It is most probable that all erythremias associated with cyanosis and dyspnea (with a theoretical exception of a neoplastic overformation of red cells, yet to be definitely shown to exist) are *compensatory* in nature (secondary to pulmonary sclerosis, emphysema, congenital heart lesions, chronic pulmonary diseases leading to insufficient oxygenation, increased resistance of the red cells with lessened oxygen-carryingcapacity, etc.).

With this point stated, the writer presents a unique case of Osler-Vaquez disease, which was under clinical observation for five years, with full autopsy and microscopic findings, in which the Vaquez syndrome of chronic cyanosis, persistent high erythremia, enlargement of liver and spleen, and hyperplasia of bone-marrow, are shown to be secondary to syphilitic disease of the pulmonary arteries (Ayerza's disease).

CASE. L. H., American, forty-three (?) years of age, laborer, was admitted to the Medical Clinic (Dr. George Dock) of the University Hospital, Ann Arbor, January 17, 1907, and was presented in the Clinic on the following day. His chief complaints at that time were difficult breathing, palpitation, blueness of skin and lips, general weakness, dropsy, and frontal and occipital headaches.

His family history, as far as known to him, was negative. His father was living; his mother had recently had an amputation of right tibia for thyroid metastasis. He was unmarried. He denied venereal disease, and claimed to drink and smoke but rarely. His health had been good up to about thirty years of age, when he began to have asthmatic attacks at night. These increased in severity and frequency. At thirty-six he had a sudden attack of apnea, and was unconscious for several minutes. From this time on he had more frequent and severe asthmatic attacks, at irregular intervals, usually at night. Four years before entrance to the hospital he first noticed blueness and swelling of his face, hands, and feet. He was told by a physician that he had "heart trouble," and under medical treatment his symptoms improved; the cyanosis disappeared and did not return until September, 1906. From this time on attacks of cyanosis, palpitation, and dyspnea became more frequent and severe, with severe frontal headaches, frequent dizziness, prominence of eyes, feeling of thoracic constriction, particularly when lying down. Pressure upon sternum produced a sensation of "smothering." He had no dysphagia, and no marked gastrointestinal disturbances.

Physical examinations by Drs. Dock and Smithies showed a man of medium build, with thin panniculus, with marked cyanosis over face and neck; hands and feet were moderately blue; color deepened when patient stood or let his arms hang down. When lying down face and neck became slaty blue, the cyanosis decreasing after several moments. Exercise and excitement increased the cyanosis. Palate and tongue were deep purple; eyes prominent, especially the right. Conjunctivæ suffused, especially on right. The pupils were of moderate size, equal and active. The external jugulars were prominent, dilated, and filled from above. There was moderate pulsation of the carotids. The thyroid was negative; no tracheal tug. Over the trunk the skin had a bluish cast. The thorax moved *en cuirasse;* respirations were shallow, not increased when resting, but rapidly increasing on slight exertion. Heart beat faintly seen in 5 i. c. s., inside the nipple. Heart rate not increased. No arrhythmia. Palpation of lungs negative. Percussion showed good resonance over lungs, low liver dullness, an abnormal area of dullness beneath the upper portion of sternum, and an atypically situated precordial outline. Splenic dullness barely made out to edge of ribs. Auscultation of lungs showed diminished vesicular over entire right side above fifth rib; below this inspiration was sharp and blowing, expiration soft and prolonged, with few piping râles. On the left side there was bronchovesicular breathing to the second rib, with increased vesicular below, with more numerous râles. Spoken and whispered voice were negative.

Auscultation of heart revealed faint sounds heard with difficulty. The first sound at apex was soft and impure; the pulmonic second moderately accentuated. Over base of heart sounds could barely be heard.

The radial pulse was slow, moderately full, fuller on left than on right. Radial arteries moderately sclerotic. The blood pressure varied on the two sides; on the left systolic was 156 mm. Hg, diastolic 109 mm.; on the right the systolic was 146, the diastolic 98 mm. (Erlanger apparatus, 12 cm. cuff).

The abdomen was somewhat distended in region of umbilicus. Lower border of liver dullness low. The liver was felt with difficulty at the end of inspiration. Splenic dullness to edge of ribs. Spleen was not palpable. No palpable mass in abdomen. Lymph nodes not enlarged.

Ophthalmologist's (Dr. W. R. Parker) examination of eyes showed a moderated conjunctival injection; marked venous congestion of retina, with edema of macular region. No hemorrhages.

Left nasal fossa was partly occluded. Examination of larynx negative.

When presented in the Medical Clinic, January 18, 1907, the red blood cell count was found to be 6,450,000, white cells 6500, and hemoglobin 100 per cent. The blood was deep red in color, flowed slowly. The red cells were normal in appearance; no nucleated forms were seen, and the differential white count was negative. Urine contained a moderate amount of albumin, and many small granular casts and cylindroids. A tentative diagnosis of "Osler-Vaquez disease" was made by Dr. Dock at this time.

Later fluoroscopic examination showed a vaguely outlined, diffuse, non-pulsating shadow above the heart, especially dense about the root of the lungs and great vessels, extending up into the neck. Heart downwards and inwards. Diaphragm low on both sides, especially so on right side.

A radiogram confirmed the fluoroscopic findings, "a mass, almost as dense as the heart, filling in the mediastinum. No definite lines of pulsation can be seen. Tumor appears to occupy both mediastinal spaces, lying in close approximation to heart, lungs, and adnexa. Points of greater or less opacity can be seen throughout the lungs, the infiltration being more marked on the left than on the right."

Course of Disease. The patient at first improved somewhat under treatment, was able to go about the hospital, his cyanosis, erythremia, and dyspnea varying in degree with conditions. About three months after entrance, while walking in the hall, he had a sudden sense of pressure in upper thorax, "felt as if he were being choked," could not breathe or speak, fell to the floor and became unconscious. When placed in bed was cyanotic and markedly dyspneic, and complained of pains in thorax. Respiratory sounds were very weak with numerous piping râles; heart sounds very weak, rate 129; systolic pressure 106, diastolic 55.

This attack was followed by a period of increasingly frequent attacks of extreme cyanosis, with more or less pronounced erythremia, marked dyspnea, associated with unconsciousness, headaches, gastrointestinal pain, and albuminuria. He was constantly cyanotic, but during the two years he was in the hospital had about seventeen attacks of extreme cyanosis ("black"), with extreme dyspnea, feeling of suffocation, precordial distress and palpitation (angina hypercyanotica), these attacks lasting for a few minutes or for several hours. During the attacks the heart rate was accelerated, going from 60 to 130. The peripheral vessels were injected, but there were no positive venous pulsations. During the attacks there was almost complete absence of breath sounds, with few high-pitched musical râles. Heart sounds became very faint. The eyegrounds always showed extreme engorgement and edema. There was no bleeding, except occasionally from nose. Enlargement of the spleen was first positively determined October 21, 1907, when it could be palpated below the edge of the ribs.

The *erythremia*, which had been noted on entrance, persisted, varying greatly, usually in proportion to the severity of the attacks of cyanosis. In over 100 blood counts taken during the 605 days in hospital, the red blood cell count only twice fell below 6,000,000, the lowest count being 5,040,000 on March 25, 1907, and the highest 9,500,000 on May 8, 1908. The average of these counts was over 8,000,000 per c.mm. Blood taken from different parts of the body showed some variation in the number of red cells. The hemoglobin was always above 100 per cent, frequently as high as 156 per cent (Miescher); with prolonged paroxysms of cyanosis and red blood cell counts of 8,000,000 per c.mm. the average hemoglobin reading was 132 per cent. The white cell count ran within normal limits, 6–10,000, and the differential white count showed little variation; at times a slight increase in eosinophiles and lymphocytes, and occasionally a few myelocytes after one of the acute attacks. Nucleated reds were occasionally noted. With the red cell count 7,400,000, specific gravity of blood was estimated at 1.062; coagulation time shortened; viscosity increased.

The patient remained in the hospital 605 days, being discharged September 12, 1908. At the time of discharge he was still showing an increase in the severity of his attacks of cyanosis, dyspnea, headaches, visual disturbances (diplopia, "turning black"), gastrointestinal symptoms (loss of appetite, intense paroxysmal pains in epigastrium radiating to lower abdomen, constipation alternating with diarrhea). His albuminuria had increased. Stools were negative. He had no dysphagia or vomiting. Temperature was never raised. The last radiograms seemed to show a gradual extension of the mediastinal mass.

Dr. Dock inclined to a diagnosis of Osler-Vaquez disease with albuminuria and chronic pericarditis; Dr. Smithies to a diagnosis of polycythemia with mediastinal tumor. The case was reported by the latter, as Case I, in an article on "Clinical Aspects of Tumors of the Mediastinum." (2) In this article, Dr. Smithies summarized the case as follows: "The case presents many of the findings of the condition of chronic cyanosis with erythremia described by Vaquez, Osler, et al. The spleen, however, is not enlarged, and the mediastinal tumor appears to be a discoverable cause for the symptoms, which is unusual or not yet reported for cases of true cyanotic polycythemia, Vaquez-Osler malady. It is not quite determined that the two conditions do not exist, but in view of the rather marked variations in the cyanosis and the red cell count, it is probable that much of the polycythemia is due to extensive pressure in the thorax on the great vessels. The changes in spleen and bone-marrow might come on later and give a characteristic picture of erythremia vera."

After leaving the hospital in 1908, the patient became a pop-corn peddler in Ann Arbor, and was seen at intervals by members of the Staff of Internal Medicine. He was still subject to attacks of cyanosis and dyspnea; but was for some time more comfortable than he had been the previous two years. He was able to work at his pop-corn business about half the time.

On April 28, 1910, his blood count was again made in the Clinic of Internal Medicine (Dr. A. W. Hewlett). The red cell count was 7,200,000, white cells 10,500, and hemoglobin 120 per cent. He was first examined by Dr. Hewlett on the next day. He found his heart enormously dilated, the lower portion of the chest retracted and immobile. Abdomen was prominent, but there was no ascites. Spleen was just palpable. Lungs showed signs of emphysema, but little bronchitis. Legs were moderately edematous. The spectroscopic examination of his fresh blood, which was dark and thick, gave the characteristic band of oxyhemoglobin. Urine showed trace of albumin and few granular casts. He appeared at intervals for examination and advice, his condition remaining about the same.

In the *Transactions of the American Ophthalmological Society*, 1910, his case was again reported, this time from an ophthalmological standpoint, by Drs. Parker and Slocum, of the University Clinic of Ophthalmology.

By this time the diagnosis of a mediastinal tumor had been completely abandoned, and the case was regarded as an uncomplicated one of "Chronic Cyanosis with Polycythemia (Osler-Vaquez Disease)." Parker and Slocum give in their article (Case I) a detailed description of the retinal appearances of intense engorgement and edema. They noted the presence of a small venous aneurysm, which later was found to have ruptured. A second retinal hemorrhage was also seen.

When patient was seen, December 2, 1910, his cyanosis was greatly increased; his hands were black.

On January 31, 1911, Dr. Hewlett found the spleen fairly easily palpable and "purpuric" spots about his joints and over his legs, some as large as a dime, and elevated. During the winter he had a very severe attack, and vomited black particles.

Readmitted to the hospital on October 24, 1911, his condition obliging him to give up work. At this time he gave his age as fifty-two. His chief complaint was still dyspnea, weakness, and cyanosis. He still denied venereal disease and alcoholism. His symptoms were about the same as when last seen. He had not lost weight; had had no blood in stools or sputum. Vision is blurred at times; and he has headaches accompanied by dizziness and nausea. Claims to sleep poorly at night; but is drowsy during the day. Sleeps between examinations. Has no thoracic pain.

Physical examination (Drs. Hewlett and Van Zwaluwenburg) showed less cyanosis than in previous admissions. Had firm, hard edema over thighs and legs, not much over back; face was puffy. Conjunctival vessels were enormously engorged; many venules were blue-black. Veins of neck were full until patient was almost upright, when they collapsed. Thorax moved poorly; there was inspiratory retraction all the way round at level of diaphragm. Abdomen was full, flat above and bulging in the flanks. Abdominal breathing marked. Percussion showed an enormously enlarged heart. Liver was a hand's breadth below the level of the ribs, reaching nearly to navel and confluent on left with splenic dullness. Lungs were nowhere very resonant; the lower borders moved slightly, but symmetrically. No localized areas of diminished resonance over front or back. Tactile fremitus was negative. Breath sounds all over the lungs were feeble, vesicular, almost inaudible over bases and back. Numerous crackling râles were present over the upper portion, large dry ones below, somewhat more abundant on right. The whole left upper portion more silent than on right. No localized voice changes. The first sound at apex was dull and distant, almost replaced by a systolic murmur; second sound poorly heard, although easily felt. The murmur waned and waxed to another maximum in the fifth i. c. s., about 2 fingerbreadths to left of sternum. It was poorly transmitted to axillæ, and not heard in back. The second sound in the tricuspid area was relatively loud. At base both sounds were distant; valvular areas could not be accurately localized; systolic murmur from below was only occasionally audible at base. No diastolic murmur. The radial pulse was small, soft, quick, and frequent. Hands were cold and moist. The liver margin was felt as a firm semi-elastic mass without a distinct edge. The spleen was just palpable in the anterior axillary line in the left hypochondrium. Otherwise belly was tympanitic. No fluid wave. Ophthalmological examination showed similar retinal engorgement and edema as before, only more marked.

Erythremia was variable as before, 7,200,000–8,760,000. The white cells ranged 7–10,600; the proportionate count was almost normal, the polynuclears being slightly increased. No nucleated forms and no myelocytes were found at this time.

The patient's condition quickly grew worse, increasing dyspnea and cyanosis, weakness, somnolence, nausea, "purpura," and finally bloody stools, blood-streaked sputum, delirium, intense cyanosis ("black"), general collapse, leading to his death on November 14, 1911.

Clinical Diagnosis. Polyglobulism, Emphysema. Cardiac hypertrophy and dilatation. Chronic passive congestion. Cardiac cirrhosis. Hemorrhage from hemorrhoids. Nephritis (?) (Dr. Hewlett).

The autopsy was performed a few hours after death.

Autopsy Protocol (Dr. Warthin). Male body, of medium frame, 172 cm. long; abdomen distended; umbilicus everted; broad epigastric angle; precordium prominent. Skin of entire body markedly cyanotic; where least cyanotic, on the upper portions of body it is yellowish blue. Hypostasis is extreme, particularly on legs. Genitals very cyanotic and slightly edematous. Numerous angiectatic warts over back, black in color. Over legs numerous circumscribed angiectatic vessels, forming blue-black spots size of pin-head to dime. No hemorrhages in skin. Skin over legs thickened and scaly. All superficial veins markedly injected. Mucous membranes intensely cyanotic. Scleræ yellowish. Musculature fair. Fair amount of panniculus. Marked edema over legs, moderate over trunk and upper portion of body. Rigor mortis present throughout. Palpation of abdomen negative. Liver and spleen could not be felt.

Head: Skull-cap moderately thick, but almost as thin as paper in left temporal region. Meningeal grooves deeply eroded, particularly that of the left middle meningeal artery. Inner table shows marked erosion. In the right temporal region there is a sharp, spine-like exostosis projecting 1 cm. from the inner table. Dural tension increased. Dura adherent all over convexity, thickened, and very tough. Adhesions between dura and arachnoid. Longitudinal sinus contains a small red clot; the veins opening into it have markedly thickened walls. Basal meninges thickened. Arachnoid over convexity thickened, and shows hyaline patches. Pial vessels enormously distended. Pacchionian bodies extremely small. Carotids and basal vessels show no sclerosis. Cerebrum intensely congested and edematous. Ventricles moderately dilated. Chorioid plexus markedly congested. Pineal gland very small. Cerebellum intensely congested and edematous. Hypophysis very small.

Spinal cord presents meningeal thickening, congestion and edema.

Main Incision: Panniculus very moist, light orange color. All blood vessels engorged with dark fluid blood. Muscles are light brownish-red, soft, and tear easily. No free gas in peritoneal cavity, and only a small amount of clear fluid (150 c.c.). Omentum below umbilicus, moderately fat, its vessels congested. Lower border of liver reaches to umbilicus in median line; in right nipple line it is a hand's breadth below edge of ribs. Spleen is large, its lower pole below edge of ribs. Stomach lying vertically, moderately distended with gas. Curious sweetish smell in abdominal cavity. Diaphragm in lower border of sixth rib on the right, in sixth i. c. s. on the left.

Sternum osteoporotic, marrow hyperplastic. No free gas in pleura cavities. Small amount of clear fluid (100 c.c.) in each cavity. Old adhesions over right apex; otherwise pleuræ are free. Lungs nearly meet in upper portion of mediastinum; their free edges show extreme emphysema. Mediastinal fat fairly abundant, very red in color. No remains of thymic tissue seen.

Heart: Of enormous size, lying almost transversely; the greater part of the right heart lies to the right of the median line, the apex in sixth i. c. s., half-way between nipple and anterior axillary lines. Apex is rounded, blunt, with no point. Pericardial sac greatly distended; no pericardial adhesions; fluid about 80 c.c., clear. All chambers of heart greatly dilated, particularly the right heart, the dilated right auricle making up one-third of the heart bulk. Right border of right auricle reaches to the right parasternal line. On cutting the inferior vena cava there is a gush of very dark fluid blood containing small jelly clots. Left and right ventricles about equally dilated; both auricles extremely dilated, the right one in a remarkable degree; the muscle fibers of its wall widely separated. The enlargement of the heart is due chiefly to dilatation; when emptied of blood its measurements are 18 x 13 x 7.5 cm., its weight 790 gm. On the table the heart flattens into a soft round disk. The subepicardial fat is increased, orange-red in color. Irregular tendinous spot over anterior wall of right ventricle. Firm thrombus in right auricular appendage. Mitral orifice admits five fingers, slight roughening and thickening of proximal edges, but no organic insufficiency or stenosis. Aortic orifice barely admits thumb; flaps negative. Tricuspid orifice greatly dilated, admitting whole hand; flaps negative. Pulmonary orifice admits three fingers, two and a half times as large as the aortic opening. Calcareous plaque in wall of pulmonary conus. Pulmonary artery enormously dilated; its wall markedly thickened, and its intima showing a condition of advanced atherosclerosis. Coronaries extremely dilated, presenting patches of sclerosis. Auricular ventricular septum intact; foramen ovale closed; no anomaly. Aorta is of medium size; its intima shows moderate sclerosis rather linear in type, with some early atheroma.

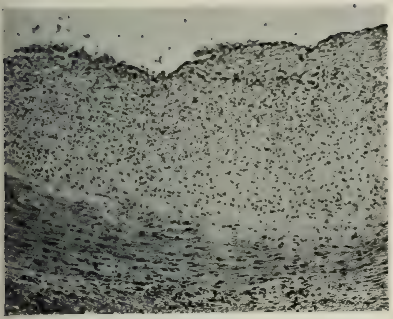

Fig. 1. Main Branch of Pulmonary Artery, Showing Extensive Atherosclerosis and Mesarteritis.

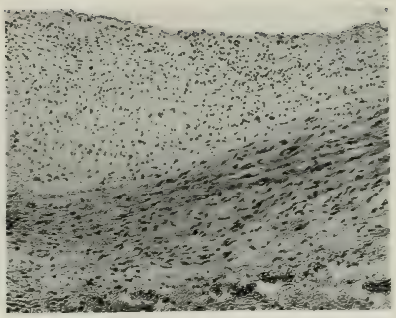

Fig. 2. Medium-sized Branch of Pulmonary Artery, at Edge of Sclerotic Patch.

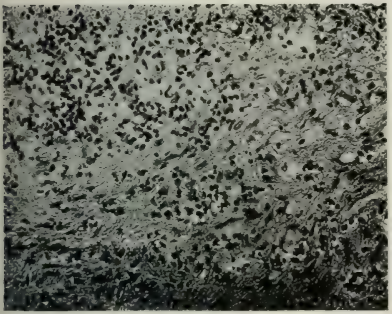

Fig. 3. Media of Main Branch of Pulmonary Artery, Showing Area of Plasma-cell and Lymphocyte Infiltration of the Media (Syphilitic Mesarteritis).

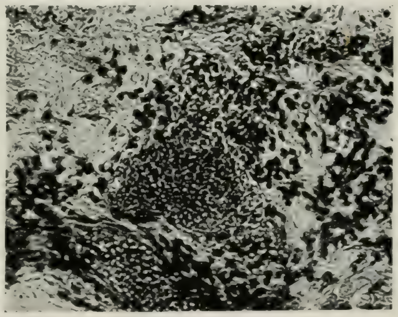

Fig. 4. Plasma Cell Infiltration about One of the Vasa Vasorum of the Main Pulmonary Artery.

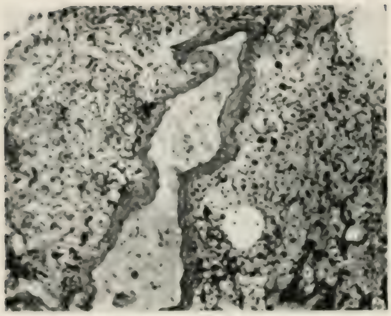

Fig. 5. Dilated and Sclerotic Smaller Pulmonary Arterial Branch.

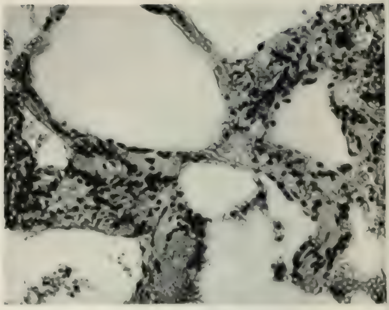

Fig. 6. Air Containing Portion of Lung, with Thick Alveolar Walls, and Some Emphysematous Alveoli.

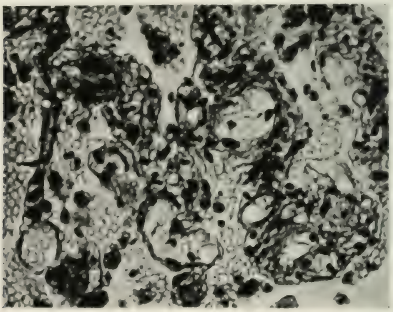

Fig. 7. Atelectatic Fibroid Area of Lung, Showing the Thickened Sinusoidal Capillaries.

Lungs: Right and left lungs weigh 625 and 675 gm. respectively. Both are very voluminous, with markedly emphysematous borders. Moderate anthracosis. Both show extreme congestion and edema. Airless areas alternate with emphysematous. All the branches of the pulmonary arteries are markedly dilated, and present an extreme condition of sclerosis and atheroma, even to the terminal branches. Lower lobes show patches of pneumonic or hemorrhagic consolidation. In the larger main branches of the pulmonary arteries the thickened intima shows porcelain-like areas, with irregular cracks and thinnings of the wall, as in syphilitic aortitis. Pulmonary veins enormously distended; their walls relatively thickened. Bronchial nodes pigmented, much congested and edematous.

Mouth and Neck Organs: Mucous membranes of mouth, pharynx, epiglottis, larynx, and trachea show extreme congestion. Thyroid is small, with small amount of colloid. The parathyroids are of normal size, and very deep red. The cervical fat has the appearance of embryonic fat. Cervical lymph nodes extremely congested.

Spleen: Free, no adhesions. Greatly enlarged before removal; much smaller after removal and bleeding; measures then 13 x 9 x 6.5 cm., and weighs 330 gm. Firm, does not flatten on pressure. Capsule thickened, with small hyaline patches. Cut surface shagreened, deep bluish-brown-red. Stroma increased; follicles not easily seen.

Adrenals: Normal in size and shape. On section show intense congestion. Medulla of right one in advanced post-mortem change.

Kidneys: Left and right measure 13.5 x 8 x 5.25 and 13 x 7.5 x 4.5 cm. respectively, and weigh 300 and 200 gm. They present similar appearances. Fatty capsules are abundant, reddish orange, resembling fetal fat in color and appearance. Fibrous capsules strip easily. Cortical surface smooth, deep purple-red, with small areas of parenchymatous degeneration in cortex. Cortex atrophic. Cut surfaces nearly uniform in color; outlines of structure cannot be made out.

Intestines: Contain a thin, soup-like, bile-stained material. No fresh blood seen. Mucosa shows extreme congestion and edema. Appendix surrounded by old adhesions. Bile passages patent. No hemorrhoids. No bleeding in rectum.

Stomach: Contains a plum-colored mucus containing some food remains. No fresh blood. Mucosa tremendously congested; chronic stasis catarrh. Pylorus thickened, firm, slight stenosis. No erosions or ulcers.

Pancreas: Large, firm, body ends abruptly without tail. Color very dark. On section shows marked congestion; lobules large with increase of interlobular connective tissue. Vessels dilated and show slight sclerosis.

Liver: Much enlarged, shows markings of ribs. After removal and bleeding measures 25 x 19 x 8 cm. and weighs 2000 gm. Capsule shows some thickening, particularly around ligaments. Lower border rather rounded. Consistence soft. On section bleeds freely. Marked "nutmeg liver." Vessels all greatly dilated. Stroma increased in patches beneath cortex. Gall bladder greatly distended. Contains thin brownish fluid.

Lymph Nodes: Mesenteric and retroperitoneal lymph nodes extremely congested, edematous, and very soft. Few atrophic hemolymph nodes, brown in color.

Prostate: Negative, except for intense congestion.

Testes: Marked congestion and edema.

Bone-marrow: Hyperplastic red marrow in sternum and ribs. In tibiæ fatty marrow.

Microscopic Findings. Brain: Extreme dilatation and congestion of all vessels, particularly of the meningeal and pial. Diffuse thickening of the inner meninges. Chronic leptomeningitis.

Cord: Marked congestion of all vessels, particularly of the meningeal. Diffuse thickening of the meninges.

Heart: Hypertrophy. Brown atrophy. Fibroid patches. Healed syphilitic myocarditis. No active areas.

Aorta: Advanced atherosclerosis with patches of active syphilitic mesaortitis.

Lungs: Extreme chronic passive congestion with numerous pigmented phagocytes, "brown induration." Main branch of pulmonary artery shows extreme atherosclerosis of the intima and inner half of the media with active patches of syphilitic mesarteritis, and plasma-cell infiltrations around some of the vasa vasorum. The intrapulmonary branches of the pulmonary artery show extreme dilatation with marked atherosclerosis of the intima and inner one-half to one-third of the media. In the branches of the second and third degree a few small plasma-cell infiltrations around the vasa vasorum are found, but the majority of these branches show no active syphilitic lesions. The smaller branches of the pulmonary vessels are extremely dilated, with thick hyaline walls showing no active process. The alveolar capillaries are greatly dilated; have thickened hyaline walls. In some areas the thickened alveolar walls appear almost like that of a çavernous angioma. In other areas the alveolar walls are atrophic, hyaline, and the capillaries almost obliterated, the alveolar partitions extending into the dilated infundibula as stiff hyaline septa. In some portions of the lung, the circulation is completely shut off and the lung is fibroid and collapsed. Hemorrhages in all stages are found everywhere throughout the lung. There is marked edema, and great numbers of pigmented phagocytes. Emphysematous areas are scattered through the indurated portions. The hyaline indurated portions of the lung are particularly the seat of anthracotic deposits. The bronchi and bronchioles are dilated and show catarrhal bronchitis. Small patches of early broncho-pneumonia are also found, particularly in the lower lobes. The pulmonary veins are extremely dilated, and show hyaline thickened walls without atheromatous changes.

Thyroid: Moderate amount of colloid. Extreme congestion of vessels.

Tongue: Numerous encapsulated trichinæ. No reaction about these.

Spleen: Extreme dilatation of blood spaces and blood vessels, many portions resembling an angioma simplex rather than spleen. The lymphoid tissue of the pulp is atrophic. Follicles are of fair size, arterioles sclerotic. The larger arteries show hyaline thickening of their walls.

Adrenals: Marked congestion, particularly in the reticular zone and medulla. Extensive medullary hemorrhage. Cortex shows extreme lipoidosis. Several small plasma-cell infiltrations in the reticular zone.

Kidneys: Extreme congestion, involving both arteries and veins. Marked hypertrophy of glomeruli, many being two to three times normal size, due to increase in size of capillary tufts. Majority of Bowman's capsules are thickened, and there is a diffuse increase of connective tissue, with many scarred glomeruli, with definite areas of chronic parenchymatous nephritis. Vessels all sclerotic. Slight cloudy swelling of convoluted tubules.

Stomach: Chronic catarrhal gastritis. Extreme congestion of both arteries and veins. In the stomach wall there are numerous areas of plasma-cell infiltration and localized induration, probably syphilitic.

Intestines: Extreme congestion of arteries and veins. Slight catarrh.

Appendix: Extreme congestion of arteries and veins. Thickening of sub-mucosa.

Pancreas: Extreme congestion of arteries and veins. Thickening of vessel walls. Fatty atrophy. Areas of marked intralobular interstitial pancreatitis with some active plasma-cell infiltrations. Many islands of Langerhans are very large and show marked dilatation of the vessels.

Liver: Extreme nutmeg liver. Atrophy and necrosis of cells of central and intermediate zones. Dilatation of all vessels with atrophy and slight cloudy swelling of liver cells. Slight fatty degeneration, particularly of the central zones of the lobules. Capsule is thickened, and the lobules just beneath are very atrophic and the periportal tissue shows proliferation, small-celled infiltration and new bile-duct formation, the picture being that of a localized atrophic cirrhosis. These cirrhotic changes are found only beneath the capsule.

Prostate and Seminal Vesicles: Extreme dilatation of all vessels with fibroid hyperplasia. In the seminal vesicles are a number of retention cysts. Spermatic and prostatic plexuses show extreme angiectasia.

Testes: Intense congestion and edema. Diminished spermatogenesis. Increase of stroma. Thickening of basement membrane. Early syphilitic orchitis fibrosa.

Lymph Nodes: All lymph nodes show excessive dilatation of the vessels, many of the retroperitoneal nodes resembling angiomas. Atrophy of lymphoid tissue and increase of stroma.

Semilunar Ganglia: Extreme dilatation of vessels, increase of interstitial tissue and pigmentation of the ganglion cells.

Bone-marrow: Tibiæ contain congested fatty marrow, with small islands of red-cell forming tissue. The sternal and rib marrow shows marked lymphoid hyperplasia.

Adipose Tissue: Reversion to fetal type. Congested and edematous.

Purpuric Spots: Telangiectasias.

Pathological Diagnosis. Plethora vera, "Osler-Vaquez disease" (erythremia; chronic cyanosis and splenic enlargement), secondary to syphilitic atherosclerosis of pulmonary arteries; emphysema and brown induration of lungs; cardiac hypertrophy and dilatation; chronic fibroid myocarditis; syphilitic aortitis; chronic interstitial gastritis; atrophy of pancreas with chronic interstitial pancreatitis; chronic syphilitic orchitis; chronic congestion of all organs; nutmeg liver; chronic splenic congestion; hypertrophy of kidneys with chronic parenchymatous nephritis; chronic leptomeningitis; multiple telangiectasias of skin; hyperplasia of bone-marrow. Latent syphilis; bronchopneumonia; old trichinosis.

Epicrisis. This case presents the complete symptom and pathologic complex of the Osler-Vaquez disease, in the form of a chronic cyanosis, high degree of erythremia and splenic enlargement, with the secondary phenomena of dyspnea, visual disturbance, gastrointestinal symptoms, general weakness, congestion, edema, etc. What is of great importance is the fact that the autopsy revealed a condition to which the Vaquez symptoms are most probably secondary. It can be very reasonably argued that, as the consequence of a widespread lesion of the pulmonary vessels, deficient oxygenation of the blood-stream was produced. As a result of the need for oxygenation secondary emphysema, hypertrophy of the right heart and increased activity of the bone-marrow developed as *compensatory conditions*. The *cyanosis* is an expression of the urgent need for oxygen; the *erythremia* is a compensation for this need; while the *splenic enlargement* is but a secondary result of the plethora and increased blood formation and destruction. The erythremia itself is brought about by an increased activity (hyperplasia) of the bone-marrow.

Further, the microscopic study of this case shows also the ultimate cause of the whole complex, in that the lesion of the pulmonary vessels presents the characteristics of a syphilitic mesarteritis. This diagnosis at present rests upon the histologic features alone. Levaditi studies of this material have just been made, but no spirochætæ have as yet been found. Additional evidence of the presence of a syphilitic infection is to be found, however, in the characteristic myocarditis, mesaortitis, pancreatitis, adrenal infiltrations, chronic orchitis, and possibly also the chronic leptomeningitis. While the hospital records yield only negative statements as to the occurrence of a syphilitic infection in this patient, a letter from Dr. Frank Smithies, now of the Augustana Hospital, Chicago, tells me that this patient was one of the first to receive a Wassermann test in his laboratory, in Ann Arbor, and that the reaction was positive. From my own standpoint, however, the histologic complex of heart, vessel, pancreas, adrenal and testicular changes can mean but one thing—a latent syphilitic infection. In the meantime, however, the search for the spirochætæ will be carried on.

The degree of arteritis, sclerosis, and atheroma of the pulmonary artery and its branches shown by this case, is, I believe, unique. I have been unable to find in the literature any description of pulmonary sclerosis in which the lesions appeared to be so severe and extensive. In the case reported by me, "Syphilis of the Pulmonary Artery: Syphilitic Aneurysm of the Left Upper Division: Demonstration of Spirochætæ Pallida in Wall of Artery and Aneurysmal Sac," (3) the sclerotic changes in the left upper branch were as marked, but in the other branches the degree of change was much less. The microscopic appearances of the pulmonary vessel lesions were identical with those in this case, and the demonstration of the spirochætæ was accomplished, both in the artery wall and in the aneurysm.

The literature of pulmonary arteriosclerosis is rapidly increasing, particularly in Spanish-American reports. In tropical countries clinical cases of pulmonary arteriosclerosis seem to be more common, and syphilis is regarded as the common etiological factor. In my previous article I collected 4 cases of gumma of the pulmonary artery, 5 cases of gummatous arteritis, 15 cases of pulmonary arteriosclerosis regarded as syphilitic from the histologic appearances or the association with other evidences of syphilis, and 51 cases of aneurysm of the pulmonary artery in which a syphilitic etiology was probable. (4) In one of the reports (5) it is stated that pulmonary arteriosclerosis is not a rare cause of fatal dropsy in Bengal, and Rogers expresses his belief that when it occurs between the ages of twenty and forty syphilis is the etiological factor.

Sanders (6) reports one case from Dürck's laboratory, and collects seven cases from the literature (Klob, Crudeli, Wolfram, Romberg, Mönckeberg's two cases, and Kitamura) of a primary sclerosis of the pulmonary arteries with associated hypertrophy of the right heart. These were the only reports of such a complex that he was able to find. The cases are incomplete, both as regards clinical history and pathological study, in so far as the question of a syphilitic etiology is concerned. It was apparently excluded or not considered. Romberg's case was characterized clinically by *dyspnea, cyanosis,* and *enlargement of liver and spleen.* No mention of the blood findings. Mönckeberg's Case I likewise showed *cyanosis,* with prominence of eyes, and edema. His second case, a man of fifty-six years, presented marked *cyanosis, edema, dyspnea, palpitation,* with *enlargement of liver.*

Although these cases are incomplete, and the condition of the blood is not stated, it seems probable that some of them, at least, fall into a class showing the syndrome of *chronic cyanosis, dyspnea, erythremia,* and *pulmonary sclerosis* recognized in Spanish-American literature as "Ayerza's Disease" (Cardiacos Negros), from the fact that in a lecture given in his clinic in 1901, Abel Ayerza, Professor of Clinical Medicine, National University of Buenos Aires, was apparently the first to recognize the clinical entity of this syndrome. As far as I have been able to discover the first published use of the term "Ayerza's Disease" is in a Doctoral Thesis, by Dr. C. A. Marty, "La Tensión Arterial en la Tuberculosis Pulmonar," Buenos Aires, 1909, p. 45, in which he says that there is a special group of cases worthy of attention because of increased pulmonary arterial tension associated with hypertrophy of the right heart, pulmonary arteriosclerosis and chronic cyanosis, described eight years previously by Ayerza as "cardiacos negros." The designation is also used by Escudero in his "Conferencias Clínicas," Buenos Aires; and by Garcia del Real, in "Tratado de Patología Médica," Madrid, 1917, IV, 495–530.

Barlaro (7) reports "A Case of Ayerza's Disease," characterized by *extreme cyanosis, asthma, intense dyspnea, cardiac hypertrophy, erythremia* (red cells 6,600,000), *enlargement of liver, spleen not palpable, Wassermann* + + + + + with *pulmonary arteriosclerosis.* He discusses the differential diagnosis of Vaquez's and Ayerza's diseases, and concludes that many cases of Vaquez's disease are really cases of Ayerza's disease. He so regards the first case reported by Vaquez, the case of Parkes Weber and Watson, Vaquez and Laubrey, Saundby and Russell, Osler (emphysema without splenic enlargement), Herringham, and others. Barlaro's point seems to be that cyanosis and bronchial-pulmonary dyspnea have nothing to do with a primary polycythemia; if they exist in association, the explanation of the condition is to be sought in conditions of the pulmonary artery (Ayerza's disease). While his case was undoubtedly one of syphilis, Barlaro is not sure that all cases of Ayerza's disease are syphilitic or secondary to a parenchymatous lesion. He draws an analogy to Raynaud's disease, and thinks "Raynaud's disease in the lungs" might account for some of the cases presenting the Ayerza syndrome.

The most complete description of the Ayerza syndrome is to be found in the monograph "Esclerosis Secundaria de la Arteria Pulmonar (Cardiacos Negros)," by F. C. Arrillaga, 1913, Buenos Aires. Eleven cases of pulmonary sclerosis with extreme cyanosis, dyspnea, and erythremia (in five cases in which a blood count was made) are described, beginning with the case seen by Ayerza in 1901. The author concludes that there can be no doubt as to the existence of a morbid entity called "cardiacos negros," and first described by Ayerza in 1901, characterized by *cyanosis, hyperglobulism, dyspnea, cough with expectoration of muco- or mucopurulent sputum, headache, angina hypercyanotica, hemoptysis, vertigo, somnolence, etc.* The patients present first a pulmonary evolution extending over a long period, then an evolution of the cardiacos negros state lasting as a rule two to five years. The patients can die sleeping, without edema, after presenting a gallop rhythm of the right heart; or death may take place from early myocardial degeneration with marked anasarca, or from a complication, the most common of which is broncho-pneumonia. The chief diagnostic points in distinguishing from other forms of cyanosis are the classical history of antecedent symptoms and the *tempo* of evolution of these, and the fact that the cyanosis is acquired, and not the final episode of an asystolic condition as in other forms of cyanosis, but is an initial symptom. The enormous hypertrophy and dilatation of the right heart is the most important objective sign in favor of a pulmonary rather than a peripheral obstruction. Radiography easily settles the diagnosis. The radiographic examination shows a low heart shadow, elongated and broadened, with rounded, elevated apex; the right border of the right ventricle extends far to the right of the sternum. Above the left border of the heart, at the base, is a convexity due to the left auricular appendage, above this the large shadow of the dilated pulmonary artery, and higher the normal shadow of the aorta. Points of differential diagnosis between acute dilatation of the heart and Ayerza's disease are shown by the *tempo* of evolution and the immense dilatation of the peripheral veins in the former condition, while the "cardiacos negros" have "almost no veins." As to the etiology, the lesions in the pulmonary vessels may be secondary to chronic pulmonary disease, bronchitis, tuberculosis, pleural adhesions, or any condition producing a final emphysema; or it may be the result of slow infections, as syphilis, or malaria, or the result of intoxications.

Summary. I am of the opinion that the clinical and pathological study of the case given in this paper separates it from the Vaquez group of erythremias into the class that Ayerza first pointed out as a distinct clinical and morbid syndrome. The long pulmonary evolution of the symptoms in the form of asthma and dyspnea, the later slow evolution of the cyanosis, erythremia, and secondary symptoms are characteristic of the Ayerza cases. The autopsy revealed a unique picture of extreme atherosclerosis of the pulmonary arteries, and the microscopic study shows the picture of a latent syphilis. The radiograms should have revealed the condition at first, had anyone at that time heard of Ayerza's disease and had thereby been enabled to make a correct interpretation of the radiographic findings. The original radiograms have disappeared, but a pencil sketch which remains of the shadows seen and interpreted as a mediastinal tumor is almost a duplicate of the radiographic illustration, Fig. IX, in Arrillaga's monograph, in which the shadow of the dilated pulmonary artery is very well shown.

The erythremia in Ayerza's disease is beyond question a secondary compensatory process, an increased functional activity of the bone-marrow to meet the deficiency in oxygen supply due to the obstructed pulmonary circulation. It is most probable that this is the case in all forms of Vaquez's disease; certainly in all of those in which there is cyanosis and dyspnea. Neither one of these symptoms belongs to a primary erythremia; and when they are present it is certain that the erythremia is secondary. Likewise, the splenic enlargement is not an essential feature of the syndrome; it is also secondary, and its appearance in the disease may be early or late, according to varying conditions of congestion and increased splenic function. Cases of congenital defects of the septum of the heart have been reported, showing the highest degree of erythremia, cyanosis, and marrow hyperplasia—the essential features of the Osler-Vaquez disease; and the same complex may arise as the result of other conditions leading to a chronic oxygen deficiency.

The Osler-Vaquez complex of cyanosis, erythremia, and splenic enlargement is a syndrome having a varied pathology and etiology, and is not a specific morbid entity. From Vaquez's disease there can be separated a group of cases showing the Vaquez syndrome associated with atherosclerosis of the pulmonary arteries, and possessing distinctive clinical and diagnostic features. To this group of cases the designation "Ayerza's disease," or, preferably, "Ayerza's syndrome," should be applied. The case described in this paper is, therefore, the first one of this type to be recognized in this country, and to be reported in English.

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Un caso de enfermedad de Ayerza; cianosis crónica, disnea y eritremia asociadas a arterioesclerosis sifilítica de las arterias pulmonares

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El hallazgo de Vaquez en 1892, del síndrome de cianosis crónica, policitemia persistente y aumento de tamaño del hígado y del bazo, con ausencia de envolvimiento cardíaco orgánico y el servicio posterior prestado por Osler al llamar la atención de los profesionales hacia este nuevo complexo sintomático, estableció para él un lugar definitivo en la nosología como enfermedad de Vaquez, de Osler, de Osler-Vaquez, eritremia, policitemia primaria, policitemia esplenomegálica, policitemia criptogénica, eritrocitosis megaloesplénica etc.

Lucas (Archives of Internal Medicine, Vol. X, 1912, pág. 597) coleccionó 149 casos indudables y 30 dudosos tomados en la literatura. Desde este trabajo, el número de observaciones publicadas ha aumentado hasta unas 200. La conclusión del resúmen de Lucas, conforme con el actual conocimiento de la enfermedad, establecía como difícil el señalamiento de una separación bien definida entre casos de policitemia probablemente secundaria pero de origen obscuro y otros de policitemia primaria o eritremia.

Las 25 autopsias publicadas, poco han aclarado la cuestión.

Desde el estudio de LUCAS, se ha tratado de determinar la naturaleza primaria o secundaria del síndrome de OSLER-VAQUEZ, observándose que éste en un número de casos creciente se encuentra asociado en tal forma a otras condiciones, que confirman la idea de su desarrollo secundario, dificultándose aún más la separación antes indicada, hasta el punto de poderse preguntar si realmente existe una enfermedad de OSLER-VAQUEZ, formándose con ella varios grupos por los más recientes escritores a causa de tal incertidumbre. El hecho de hallarse casos publicados bajo títulos como "Policitemia sin esplenomegalia", "Policitemia sin cianosis", "forma frustrada", "forma congénita", forma cardíaca", "enfermedad de Geisboek", "enfermedad de Blumenthal", revela la confusión dentro del esfuerzo realizado para fijar tal complejo sintomático como entidad morbosa bien limitada, no obstante los ensayos hechos para determinar las formas según el número de hematíes, estado de la médula ósea, etc.

Ahora bien, ¿existe una eritremia primaria?; nosotros creemos que no, en los casos en que aparezca cianosis crónica y dísnea. Porque en caso de poliglobulia absoluta, habría de existir cianosis o dísnea? Por otra parte, hay una razón para que la cianosis crónica y dísnea, desarrollen una eritremia crónica; es más probable que todas las eritremias asociadas a cianosis y dísnea (con la sola excepción teórica de una superproducción neoplásica de glóbulos rojos, aún no definitivamente comprobada) sean compensatorias en su naturaleza, secundarias a esclerosis pulmonares, enfisema, lesiones cardíacas congénitas, afección pulmonar crónica, etc., que conducen a oxigenación deficiente, resistencia aumentada de los hematíes con disminución de su capacidad de transportar oxígeno, etc.

Una vez establecido ésto, vamos a presentar un caso único de enfermedad de Osler-Vaquez que estuvo en observación clínica por espacio de cinco años, del que hicimos la autopsia completa y hallazgos microscópicos y en el que el síndrome de cianosis crónica persistente, eritremia intensa, aumento de híga do y bazo e hiperplasia de la médula ósea, puede considerarse secundario a una lesión sifilítica de las arterias pulmonares.

Historia clínica

L. H., norteamericano, 43 (?) años de edad, obrero; fué admitido en Ann Arbor Clínica Médica del Dr. George Dock en el Hospital de la Universidad, el 17 de Enero de 1907; se quejaba principalmente de dificultad al respirar, palpitaciones, azuleamiento de labios y piel, decaimiento general, hidropesia y cefalalgia frontal y occipital.

Los antecedentes familiares conocidos eran negativos, viviendo su padre aún y habiendo sufrido su madre recientemente la amputación de la pierna derecha por una metástasis tiroidea.

Datos personales. — Soltero. Sin enfermedades venéreas anteriores, al decir suyo, y bebiendo y fumando raramente. Salud excelente hasta los 30 años, en que comenzó a sufrir ataques de asma nocturnos, que fueron aumentando en intensidad y frecuencia, llegando a padecer a los 36 años un ataque repentino de apnea, con inconsciencia durante algunos minutos; de este tiempo en adelante ha continuado el asma en progresión creciente, preferentemente nocturna y con intervalos irregulares. En 1903 se dió cuenta del tono azulado e hinchazón de cara, manos y pies. Diagnosticado de cardíaco, con un tratamiento apropiado, mejoraron sus molestias y desapareció la cianosis, para reaparecer de nuevo en Setiembre de 1906, con los restantes síntomas intensificados, fuerte cefalalgia frontal, frecuentes vértigos, prominencia de las bulbos oculares, sensación de opresión torácica exacerbada en decúbito supino y sofocación a la presión esternal. No tiene disfagia ni marcadas alteraciones gastrointestinales.

Se practicó el examen médico por los Dres. Dock y Smithies, con el siguiente resultado: Hombre de mediana robustez, panículo adiposo escaso, señalada cianosis en cara y cuello, más moderada en pies y manos, acentuándose cuando el enfermo se ponía de pie o dejaba colgar sus brazos; al acostarse, cara y cuello tomaban un tono apizarrado, que decrecía transcurrido algún tiempo; por el contrario lo exageraban el ejercicio y la excitación. Lengua y bóveda de la boca de color purpúreo; derrame conjuntival y ocular, sobre todo en el lado derecho; pupilas de tamaño moderado, iguales y activas; yugulares externas prominentes, dilatadas y llenas desde lo más alto; pulso moderado de las carótidas; tiroides negativo; no existía tiro traqueal; sobre el tronco la piel aparece ligeramente azulada. El tórax se mueve en coraza; las respiraciones eran superficiales, sin aumento durante el descanso, pero sí con el más ligero esfuerzo; el corazón late débilmente en el quinto espacio intercostal, por dentro de la línea mamilar; no existía aumento de las pulsaciones ni arritmias.

La palpación del tórax es negativa; por percusión se encuentra resonancia, con macidez hepática baja y un área de macidez anormal en la parte superior del esternón; situación atípica del límite precordial.

Por auscultación, disminución del murmullo vesicular en el lado derecho sobre la quinta costilla y por debajo, inspiración aguda y soplante y espiración blanda y prolongada, con algunos estertores débiles; en el lado izquierdo, respiración bronco-vesicular hasta la segunda costilla y por debajo más marcadamente vesicular con numerosos estertores. Voz hablada y cuchicheo negativos.

Los ruidos cardíacos son débiles, oyéndose con dificultad; el primer sonido del vértice es blando y confuso, el segundo pulmonar moderadamente acentuado. El pulso radial es lento y bastante lleno, más a la izquierda y las arterias radiales con ligera esclerosis. Midiendo la presión con el aparato de Erlanger, señalaba en la izquierda 156 mm. de mercurio la sistólica y 109 la diastólica y en la derecha 146 y 98 respectivamente.

El abdomen aparece algo distendido en la zona umbilical. El hígado se toca con dificultad al terminar la inspiración. La macidez esplénica llega al borde costal, pero el bazo no es palpable. No hay nódulos linfáticos apreciables.

El examen oftalmológico (Dr. W. R. Parker) indica inyección conjuntival moderada; congestión venosa retiniana con edema de la región macular; no existen hemorragias. La fosa nasal izquierda está ocluída parcialmente.

Al ingresar en el Hospital Universitario, el análisis sanguíneo daba 6.450.000 hematíes, 6.500 leucocitos y 100 por 100 de hemoglobina; los glóbulos rojos eran normales en apariencia, sin existir formas nucleadas; el recuento diferencial de los blancos era negativo; la sangre de color rojo oscuro fluía lentamente. La orina contenía ligera cantidad de albúmina con algunos restos granulares y cilindroides.

Entonces el Dr. Dock, a base de los anteriores datos, hizo un primer diagnóstico de enfermedad de Osler-Vaquez.

Más tarde, el estudio radioscópico mostró una sombra no pulsátil, ni bien delimitada, difusa sobre el corazón, que quedaba dentro y debajo y densa en la raíz de los pulmones y sobre los grandes vasos, extendiéndose hacia el cuello y encontrándose el diafragma bajo en ambos lados y sobre todo en el derecho. En la radiografía aparece una masa, casi tan densa como el corazón, que llena ambos espacios mediastínicos, muy aproximado al corazón, pulmones y anexos; además, se ven puntos de infiltración en los pulmones, más marcados en el lado izquierdo.

Curso de la enfermedad. — El paciente mejoró ligeramente al principio bajo el tratamiento, siendo capaz de caminar y atenuándose su cianosis y disnea, hasta un día (tres meses después de su entrada) en que paseando, tuvo una sensación repentina de opresión en la parte superior del tórax, cayó al suelo sin poder respirar ni hablar y quedó inconsciente. Llevado a la cama, quedó cianótico y muy disnéico, quejándose de dolor torácico; los sonidos cardíacos, en número de 129, eran muy débiles, y lo mismo los respiratorios, con estertores sibilantes. La presión sistólica era de 106 y de 55 la diastólica. Este ataque fué seguido de un período en que los accesos de extrema cianosis se sucedían, con disnea marcada, inconsciencia, dolor de cabeza, molestias gastrointestinales y albuminuria; se repitieron 17 veces en dos años de internación hospitalaria, duvando desde unos minutos a varias horas, con sensación de ahogo, palpitaciones, taquicardia (de 60 a 130 latidos), inyección de los vasos periféricos — sin pulsaciones venosas —, debilitamiento grande de los ruidos respiratorios con algunos "rales" musicales y anfóricos de alta tonalidad; la región ocular siempre ingurgitada y edematosa; como manifestación hemorrágica, solamente alguna epistaxis ocasional; la esplenomegalia fué determinada positivamente por vez primera en 21 de Octubre de 1907, pudiendo palparse el bazo bajo el reborde costal.

Persiste la eritremia, cuya intensidad varía proporcionalmente a la importancia del acceso; en el Hospital se le hicieron un centenar de recuentos globulares, con el término medio de 8.000.000 de hematíes; en dos fué inferior a seis millones, siendo el más bajo 5.040.000 (Marzo, 25, 1907) y el más elevado de 9.500.000 (Mayo, 8, 1908) y variaba el número de glóbulos rojos, según la región de donde se tomaba la sangre; la media de hemoglobina llegaba al 132/100 alcanzando en los paroxismos de cianosis hasta el 156/100; la variación leucocitaria encajaba dentro de los límites normales de seis a diez mil y su fórmula también se mantenía bastante constante, con ligeras eosinofilia y linfocitosis en ciertas ocasiones y escasos mielocitos después de alguno de los ataques. Con 7.490.000 hematíes, el peso específico de la sangre fué de 1.062, su viscosidad mayor y el tiempo de coagulación más corto.

El 12 de Setiembre de 1908 fué dado de alta el paciente a petición suya, no obstante su estado, pues persistían los trastornos arriba descritos, con alteraciones visuales (diplopia, "turning black"), gastrointestinales (anorexia, intensos dolores paroxísmicos del epigastrio radiando al bajo abdomen, constipación alternando con diarrea) y aumento de la albuminuria; la temperatura era normal, el examen de las heces fué negativo y no existían ni disfagia ni vómitos; las últimas radiografías mostraban aumento gradual de la masa mediastínica.

El Dr. Dock se inclinaba al diagnóstico de enfermedad de Osler Vaquez, con albuminuria y pericarditis crónica, en tanto que para el Dr. Smithies se trataba de un caso de policitemia con tumor de mediastino y como tal lo publicó bajo el título "Clinical Aspects of Tumors or the Mediastinum" (Journ. Am. Med. Assoc., 1908, vol. 51, pág. 897), resumiéndolo en la forma siguiente: "La observación ofrece muchos de los síntomas de la cianosis crónica con eritremia descrita por Vaquez, Osler, etc. Sin embargo, el bazo no aparece ensanchado y el tumor mediastínico pudiera ser la causa rara y no publicada aún, para casos de verdadera policitemia cianótica o enfermedad de Osler-Vaquez. Todavía no está totalmente determinado el que las dos condiciones no coexistan, pero en vista de las marcadas variaciones de la cianosis y del recuento globular, es probable que en mucho se deba la policitemia a la presión extensa en el tórax sobre los grandes vasos, pudiendo sobrevenir posteriormente los cambios en el bazo y médula ósea que dan el tipo característico de verdadera eritremia".

Una vez dado de alta, el enfermo se dedicó a vendedor ambulante en Ann Arbor y con intervalos fué visto en la sección de Medicina Interna, encontrándose más aliviado. El 28 de Abril de 1910 se le hizo un análisis de sangre en la clínica del Dr. A. W. Howlett, dando 7.200.000 hematíes, 10.500 leucocitos y 120|100 de hemoglobina; al examen el corazón aparece enormemente dilatado y la parte baja del pecho retraída e inmóvil; pulmones con señales de enfisema y escasa bronquitis. Abdomen prominente sin ascitis; bazo palpable. Piernas moderadamente edematosas; orina con trazas de albúmina y algunos residuos granulares. El examen espectroscópico de la sangre fresca, que es obscura y espesa, da la banda típica de oxihemoglobina.

En "Transaction of the American Ophtalmological Society", 1910, fué publicado el caso, desde el punto de vista de sus alteraciones oculares, por los Dres. Parker y Slocum, de la Clínica Oftalmológica de la Universidad de Michigan; ya en este tiempo se abandona el diagnóstico de tumor de mediastino, ateniéndose exclusivamente al de enfermedad de Osler-Vaquez. Parker y Slocum, describen detalladamente en su artículo el ingurgitamiento y edema retilianos y un pequeño aneurisma venoso, que más tarde se vió en estado roto.

El 31 de Enero de 1911, el Dr. Hewlett encontró aumento de cianosis, manos negras y manchas elevadas de tono purpúreo intenso en las piernas y en la piel de las articulaciones, algunas de ellas del tamaño de una moneda de diez centavos; en uno de los accesos vomitó partículas negruzcas.

Fué readmitido en el Hospital el 10 de Octubre de 1911 y por entonces su edad frisaba con los 52 años; la sintomatología era aproximadamente la misma que la observada últimamente; no ha perdido de peso ni tiene dolor torásica, pero continúan las cefalalgias y vértigos, duerme poco por lo noche, siendo grande, en cambio, la somnolencia diurna. Pasa a observación de los doctores Hewlett y Zwalnwenburg, que encuentran menos cianosis que en las anteriores hospitalizaciones del paciente, edema firme en muslos y piernas y escaso en la espalda, cara abotargada; los vasos conjuntivales enormemente inyectados y muchas venillas de color azul oscuro; en decúbito supino las venas del cuello están llenas, colapsándose al incorporarse el sujeto.

El tórax se mueve pobremente; hay retracción inspiratoria de todo el contorno al nivel del diafragma. El abdomen muy lleno, aplastado en la parte media y desplazándose a los costados; señalada respiración abdominal.

La percusión muestra enorme ensanchamiento del corazón; el hígado sobrepasa las costillas en la anchura de una mano y su macidez alcanza casi el ombligo y confluye a la izquierda con la esplénica. El examen táctil del pecho es negativo; los bordes pulmonares inferiores se mueven ligeramente pero con simetría y no existen áreas de resonancia disminuída en la parte anterior ni en la posterior.

Los ruidos respiratorios son muy débiles y casi inapreciables en la base y zona posterior; en la superior muchos estertores crepitantes, secos por debajo y más abundantes a la derecha, donde los ruidos son más intensos. No son apreciables modificaciones en la voz.

El primer sonido de la punta del corazón es distante y lleno, casi reemplazado por un murmullo sistólico; el segundo murmullo, aunque débil, bien perceptible; aquel murmullo se atenúa y luego va "in crecendo" para alcanzar otro máximo en el quinto espacio intercostal, dos dedos a la izquierda del esternón, apenas se transmite a la axila y no es posible oirlo en la espalda. El segundo ruido en el área tricúspidea está relativamente alto; las localizaciones valvulares, no son realizables con exactitud; no existe murmullo diastólico. El pulso radial es corto, blando, rápido y frecuente.

Las manos están frías y húmedas. El vientre timpánico, sin fluctuaciones de líquidos; no se puede delimitar el borde hepático, que da la impresión de una masa firme y semi-elástica; el bazo es palpable en el hipocondrio izquierdo, en la línea axilar anterior.

Los análisis de sangre arrojan resultados análogos a los anteriores, con algún aumento de los polinucleares, pero sin que existan ya formas nucleadas ni mielocitos.

El estado del enfermo empeora con rapidez de día en día, intensificándose visiblemente sus trastornos; aparecen heces y esputos sanguinolentos, la cianosis llega a un tono negruzco, sobrevienen el delirio y un colapso general, que ocasionan su muerte el 14 de Noviembre de 1911.

Diagnóstico clínico. — Poliglobulia; enfisema; hipertrofia y dilatación cardíacas; congestión pasiva crónica; cirrosis cardíaca; hemorroides; nefrittis ? (Dr. Hewlett).

Protocolo de la autopsia, realizada por nosotros pocas horas después de la defunción.

Cuerpo masculino de un metro setenta y dos centímetros de estatura; abdomen distendido, ombligo invertido, amplio ángulo epigástrico, prominente región precordial. Gran cianosis en toda la piel, que toma una coloración azulado-amarillenta en la parte superior del cuerpo. Extrema hipostasis sobre todo en las piernas. Genitales muy cianótico y ligeramente edematosos. Múltiples verrugas angiestásicas en la espalda; en las piernas numerosos vasos angiestásicos circunscriptos, formando manchas de tamaño variable desde una cabeza de alfiler a una moneda de diez centavos; no hay hemorragias cutáneas. Venas superficiales muy inyectadas; cianosis de las mucosas; esclerótica amarillenta. Musculatura bien conserva-da, así como el panículo. Edema marcado de las piernas y moderado del tronco y regiones superiores. "Rigor mortis". Palpación negativa de hígado y bazo.

Cabeza: Tapa del cráneo de espesor medio, adelgazándose como un papel en la región temporal. Profundas impresiones de las meníngeas, especialmente de la arteria meningea media. Tabla interna con considerable erosión. En la región temporal derecha, aguda exóstosis que se proyecta un centímetro de la tabla interna. Aumento de la tensión dural; la dura gruesa, fuerte, adherida en la convexidad y a la aracnoides; el seno longitudinal contiene un pequeño coágulo rojo, y las venas que en él se abren ofrecen las paredes espesadas. Meníngeas basales gruesas; aracnoides engrosadas en la convexidad, mostrando placas hialinas. Los vasos de la pía-madre muy distendidos; corpúsculos de Paccioni pequeños; no hay esclerosis de los vasos basales. Cerebro intensamente congestionado y edematoso; ventrículos algo dilatados; plexo-coroide con gran congestión; glándula pineal muy reducida, lo mismo que la hipófisis; las alteraciones del cerebelo son análogas a las del cerebro. Médula espinal con edema, congestión y engrosamiento meníngeo.

Incisión principal. — Panículo muy húmedo, de color anaranjado y con los vasos llenos de una sangre oscura y fluída; músculos de aspecto moreno-rojizo, blandos y fácilmente desgarrables. No existe gas libre en la cavidad peritoneal y sí tan sólo 150 c.c. de un líquido claro; el omento por debajo del ombligo, moderadamente graso y con congestión vascular. El borde inferior del hígado alcanza el ombligo en la línea media; en la línea mamilar derecha está por debajo de las costillas en la anchura de una mano. El bazo es grande y su polo inferior desciende del reborde costal. El estómago queda vertical y ligeramente distendido por el gas. Extraño olor a sudor en la cavidad abdominal. El diafragma corresponde al borde inferior de la sexta costilla a la derecha y al sexto espacio a la izquierda.

Esternón osteoporótico, con hiperplasia medular. No existe gas libre en las cavidades pleurales, cada una de las cuales encierra unos 100 c.c. de substancia líquida; pleura libre, a excepción del ápice derecho que presenta adherencias viejas. Los bordes libres de los pulmones enfisematosos y éstos casi se tocan en la parte superior del mediastino; grasa mediastínica abundante y rojiza. No se encuentran restos tímicos.

El corazón es enorme y casi transversal, quedando la mayor parte del corazón derecho a la derecha de la línea media y el apex en el sexto espacio entre la axilar anterior y la mamilar; éste es redondeado. Saco pericárdico sin adherencias, muy distendido y con 80 c.c. de fluído claro. Gran dilatación de las cavidades del corazón, especialmente de las derechas, ocupando la aurícula de este lado un tercio de la masa total y llegando su borde externo a la línea paraesternal derecha; a la sección de la cava inferior, brota sangre oscurísima y fluída, conteniendo pequeños coágulos. El ensanchamiento del corazón es debido principalmente a la dilatación; vacío, tiene por dimensiones 18×13×7,5 centímetros y pesa 790 gramos; en la mesa queda aplastado en un disco blando; la grasa subpericárdica es anaranjada y abundante; hay una mancha irregular en la pared anterior del ventrículo derecho y un trombo-forme en el apéndice auricular del mismo lado. El orificio mitral, sin insuficiencia orgánica ni estenosis, admite cinco dedos, es algo áspero y de bordes proximales gruesos; el aórtico admite el pulgar holgadamente; el tricúspideo muy dilatado, de válvulas negativas, permite introducir toda la mano; en el pulmonar pueden meterse tres dedos y sus dimensiones son dos y media veces las del aórtico. Hay placa calcárea en la pared del cono pulmonar; la arteria pulmonar dilatadísima, ofrece paredes gruesas y su íntima muestra avanzada arteroesclerosis. Placas escleróticas en las corolarias dilatadas; secto aurículo-ventricular intacto; forámen oval cerrado; no hay anomalías. Aorta de tamaño medio, con esclerosis moderada de tipo linear en la íntima y algo de ateroma temprano.

Los pulmones pesan 625 gramos el derecho y 675 el izquierdo, y ambos están congestionados y edematosos; moderada antracosis; alternan áreas sin aire con otras enfisematosas; todas las ramas de las arterias pulmonares, aparecen muy dilatadas y con esclerosis y ateroma señaladísimos, hasta en las terciarales, mostrando las mayores en los engrosamientos de la íntima, zonas aporcelanadas, con hendiduras irregulares y adelgazamiento de la pared como en la aortitis sifilítica. Las venas pulmonares muy distendidas y con paredes relativamente espesas. Nódulos bronquiales pigmentados.

Boca y cuello: Mucosas de boca, faringe, epiglotis, laringe y tráquea con extrema congestión. Tiroides pequeño, con escaso coloide. Paratiroides de tamaño normal e intensamente rojos. Grasa cervical con apariencia de embrionaria. Nódulos cervicales muy congestionados.

Bazo: Libre; muy grande antes de su extración, disminuyendo de volumen una vez desangrado, midiendo entonces 13 × 9 × 6,5 cms. y pesando 330 grs. Firme a la presión; cápsula engrosada, con pequeñas placas hialinas. Al corte superficie chagrinada de color moreno azulado; estroma aumentado; se aprecian marcadamente los folículos.

Suprarrenales: Normales en tamaño y forma. A la sección, congestión intensa. En la derecha, la médula presenta avanzadas lesiones post-mortem.

Riñones: Miden respectivamente el derecho e izquierdo, 13,5 × 8 × 5,25 y 13 × 7,5 × 4,5 cms. y pesan 300 y 200 gramos; el aspecto es análogo en los dos; la grasa capsular es abundante y recuerda la fetal; las cápsulas se desgarran fácilmente. Corteza atrófica; superficie cortical lisa, de color rojo purpúreo, con pequeñas áreas de degeneración parenquipúreo, con pequeñas áreas de degeneración parenquimatosa; al corte, superficie uniforme que no permite darse cuenta del aspecto estructural.

Intestinos: Contienen un material de consistencia de papilla, teñido por la bilis; mucosa congestionada y edematosa; no se ve sangre fresca. El apéndice está rodeado de adherencias antiguas; conductos biliares bien aparentes; no hay hemorroides y el recto no sangra.

Estómago: Contenido de color ciruela, con algunos restos alimenticios; mucosa congestionada; no hay sangre reciente; píloro grueso, firme, ligeramente estenosado; no se ven erosiones ni úlceras.

Páncreas: Grande, firme, sin cola, pues el cuerpo termina con todo su espesor. Muy oscuro; congestionado al corte; lóbulos grandes, con aumento del conectivo interlobular; vasos dilatados, con alguna esclerosis.

Hígado: Muy ensanchado, muestra la impresión de las costillas; removido de su sitio y sangrado, mide 25×19×8 cms. y pesa 2000 gramos; cápsula un tanto engrosada, particularmente alrededor de los ligamentos; borde inferior bastante redondeado; consistencia blanda; a la sección sangra libremente; aspecto moscado; gran dilatación vascular; placas subcorticales. Vesícula biliar sumamente distendida, llena de un líquido moreno.

Nódulos: linfáticos mesentéricos y retroperitoneales muy congestionados, edematosos y blandos; escasos nódulos hemolinfáticos atróficos, de color oscuro.

Próstata: Sólo presenta una intensa congestión.

Testículos: Edematosos y congestionados.

Médula ósea: Es roja e hiperplástica en esternón y costillas y grasa en la tibia.

Examen microscópico

Cerebro: Dilatación y congestión vascular, sobre todo en los vasos meníngeos (pía-madre). Engrosamiento difuso de las meninges internas. Leptomeningitis crónica.

Médulas: Alteraciones idénticas a las anteriores en vasos y menínges.

Corazón: Hipertrofia; atrofia morena; placas fibroides; miocarditis luética cicatrizada; no hay áreas activas.

Aorta: Avanzada ateroesclerosis, con puntos de sífilis activa. Mesoarteritis.

Pulmones: Extrema congestión pasiva crónica, con abundantes fagocitos pigmentados. "Induración morena". La rama principal de la arteria pulmonar con ateroesclerosis de la íntima y porción interna de la media; zonas activas de mesoarteritis sifilítica; infiltrado de elementos plasmáticos alrededor de los vasa-vasorum. En las ramas intrapulmonares, notable dilatación con ateroesclerosis de la íntima y mitad o tercio interno de la media; en las ramas de segundo o tercer grado, pequeños infiltrados de plasmacellen, sin lesiones. Las ramas más pequeñas, muy dilatadas, con paredes gruesas, hialinas, que no muestran procesos activos, lo mismo que los capilares alveolares. En ciertas áreas, parecen angiomas cavernosos, las gruesas paredes alveolares, mientras que en otras son atróficas, hialinas, con capilares casi obliterados, extendiendose estos tabiques rígidos, en los infundíbulos dilatados. En algunas zonas, la circulación se extinguió y el pulmón se muestra fibroso y colapsado. Se encuentran hemorragias en diversos estados,, esparcidas por todo el pulmón, edema y numeroses fagocitos pigmentados entremezclándose áreas enfisematosas con otras induradas y siendo las porciones hialinas, el asiento especial de los depósitos antracólicos. Bronquios y bronquiolos dilatados, con bronquitis catarral, pudiendo verse zonas de bronconeumonía temprana, en particular en los lóbulos inferiores. Los demás vasos, dilatados y con paredes hialinas, sin cambios ateromatosos.

Tiroides: Moderado conjunto de coloide. Congestión vascular intensa.

Lengua: Numerosas triquinas encapsuladas, sin reacción.

Bazo: Enorme dilatación de las espacios y vasos sanguíneos, recordando en mucho al angioma simple; el tejido linfoide de la pulpa es atrófico; los folículos ofrecen regular tamaño; hialización en las paredes de las arterias mayores y esclerosis de las arteriolas.

Suprarrenales: Señalada congestión, sobre todo en la zona reticular y médula. Extensa hemorragia medular; lipoidosis cortical; pequeñas infiltraciones plasmáticas en la zona reticular

Riñones: Congestión intensa envolviendo arterias y venas. Hipertrofia de los glomérulos, muchos de los cuales son dos o tres veces mayores que los normales, por el aumento de los penachos capilares; casi todas las cápsulas de Bowmann engrosadas a causa del aumento difuso del conectivo; bastantes glomérulos forman zonas cicatrizadas, con áreas de nefritis parenquimatosa crónica; esclerosis vascular; ligera hinchazón turbia de los tubos contorneados.

Estómago: Gastritis catarral crónica. Considerable congestión de los vasos. En la pared gástrica, localizaciones de induración e infiltración plasmática, probablemente de tipo luético.

Intestinos: Ligero catarro. Estado congestivo de arterias y venas. Engrosamiento de la submucosa er el apéndice.

Páncreas: Enorme congestión de los vasos y engrosamiento de sus paredes. Atrofia grasa. Zonas de pancreatitis intersticial con alguna infiltración de plasmacellen. Muchos islotes grandes y con dilatación vascular.

Hígado: Claramente moscado. Atrofia y necrosis celular en las zonas central e intermedia; dilatación de los vasos, con atrofia e hinchazón turbia de los elementos hepáticos; ligera degeneración grasa, especialmente en el centro de los lóbulos; cápsula gruesa y lóbulos subcapsulares atróficos; el tejido periportal, muestra proliferación, infiltrado de pequeñas células y formación de pequeños conductillos biliares; aspecto análogo al de una cirrosis atrófica localizada debajo de la cápsula.

Próstata y vesículas seminales. Gran dilatación vascular con hiperplasia fibroide; en las vesículas cierto número de quistes de retención; plexos espermático y prostático, angiestásicos.

Testículos: Extremados, congestión y edema. Disminución de la espermatogenesis;; aumento del estroma; engrosamiento de la membrana basal; orquitis fibrosa sifilítica temprana.

Nódulos linfáticos: Todos con vasos muy dilatados, recordando angiomas muchos de los retroperitoneales; atrofia del tejido linfático y aumento del estroma.

Ganglios: semilunares. Considerable dilatación vascular, aumento del tejido intersticial y pigmentación de los elementos ganglionares.

Médula ósea: En la tibia, médula grasa congestionada, con pequeños islotes de células rojas formando tejido; la médula esternal y costal, muestra hiperplasia linfoide.

Tejido adiposo: Reversión al tipo fetal. Congestión y edema.

Manchas purpúreas: Telangiectasias.

Diagnóstico anatomo-patológico. — Plétora vera. Enfermedad de Osler Vaquez (Eritremia, cianosis crónica y esplenomegalia) secundaria a ateroesclerosis sifilítica de la arteria pulmonar. Enfisema e induración morena de los pulmones. Hipertrofia y dilatación cardiaca. Miocarditis fibroide crónica. Aortitis sifilítica. Gastritis crónica intersticial. Atrofia del páncreas con pancreatitis crónica intersticial. Orquitis sifilítica crónica. Congestión crónica de todos los órganos. Hígado moscado. Hipertrofia renal con nefritis parenquimatosa crónica. Leptomeningitis crónica. Telangiectasias cutáneas múltiples Hiperplasia de la médula ósea. Triquinosis antigua.

Consideraciones

Este caso presenta el síndrome clínico completo y el complejo histopatológico de la enfermedad de Osler-Vaquez, con los fenómenos secundarios de disnea, alteraciones visuales, trastornos gastrointestinales, debilidad general, congestión, etc. Es de suma importancia el hecho, revelado por la autopsia, del carácter secundario de los síntomas de Vaquez; pudiera arguirse razonablemente, que a consecuencia de una extensa lesión de los vasos pulmonares, se produjo deficiente oxigenación de la corriente sanguínea, y como condiciones compensatorias, enfisema, hipertrofia del corazón derecho y aumento en la actividad de la médula ósea. La cianosis indica la necesidad de oxígeno; la eritremia compensa tal necesidad; la esplenomegalia es consecuencia de la plétora, de la mayor formación sanguínea y de su destrucción; la misma eritremia es originada por el aumento de actividad de la médula ósea. Asimismo el estudio microscópico del caso muestra como causa última la lesión de los vasos pulmonares, con caracteres de mesoarteritis sifilítica histológicamente, pues no hallamos espiroquetas, habiéndolos buscado con el método Levaditi; comprueban tal infección luética, la miocarditis, mesoaortitis, pancreatitis, infiltraciones de las suprarrenales, orquitis crónica y acaso la leptomeningitis crónica. Los Archivos del Hospital, arrojan resultados negativos acerca de una posible sífilis de este enfermo, pero sin embargo, el Dr. Fr.

Smithies *actualmente en el Hospital Augustano de* Chicago, nos comunica que fué uno de los primeros sujetos a quienes se practicó la reacción Wassermann en su Laboratorio de Ann Arbor y que el resultado fué positivo. No obstante ésto, bajo nuestro punto de vista, el complejo anatomo-patológico de los cambios del corazón, vasos, páncreas, suprarrenales y testículos, significa tan solo una infección sifilítica latente, pero hemos de continuar buscando el espiroqueto. Juzgamos únicos los grados de arteritis, esclerosis y ateroma de la pulmonar y sus ramas, halladas en este caso; no hemos encontrado en la literatura médica, una descripción de esclerosis de la pulmonar en que las lesiones fueran de tal intensidad y extensión; en la observación que publicamos, bajo el epígrafe: "Syphilis of the Pulmonary Artery; Syphilitic Aneurysma of the Left Upperdiv.; Demonstration of Spiroch. Pall. in Wall of Artery and Aneurysmal Sac", (Amer. Journ. of Syphilis, Vol. I, 1917), los cambios escleróticos en la rama izquierda superior, fueron muy marcados, pero no tanto en las restantes; el aspecto microscópico de las lesiones, eran idénticas a las del caso actual y hallamos el espiroqueto en la pared arterial y en el aneurisma.

La literatura de la arterioesclerosis pulmonar aumenta notablemente, en especial en las publicaciones hispano-americanas, pareciendo ser más comunes tales lesiones en aquellas comarcas y siendo primordial el papel de la lúes en su etiología. En nuestro anterior artículo coleccionamos cuatro casos de goma de la arteria pulmonar, cinco de arteritis gomosa, quince de arterioesclerosis pulmonar — consideradas como sifilíticas por sus apariencias histológicas o por su asociación con otros síntomas — y cincuenta y uno de aneurisma de la pulmonar de probable etiología avariósica.

En una publicación de Rogers, de 1909, se dice que la arterioesclerosis pulmonar, no es causa rara de hidropesía en Bengala, creyendo que cuando ello ocurre entre los veinte y los cuarenta años de edad, es la sífilis el factor etiológico. Sanders (Arch. of Internal Medicine, Vol. III, 1909, pág. 257) describe un caso del Laboratorio de Dürck y cita siete nas (Klob, Crepelli, Wolfram, Romberg, Kitamura y dos de Monckeberg) de esclerosis primaria de las arterias pulmonares, asociada a hipertrofia del corazón derecho y ellos son los únicos que hemos podido revisar con tal conjunto, todos ellos son incompletos tanto en clínica, como en histopatología, en lo que se refiere a la sífilis como factor etiológico, pues no se toma en consideración; el de Romberg, se caracterizaba clínicamente, por dísnea, cianosis, hepato y esplenomegalia, sin mencionar estudios en la sangre; Monckeberg en el primero señala cianosis, prominencia ocular y edema y en el segundo cianosis pronunciada, dísnea, edema, palpitaciones y hépatomegalia. No obstante el escaso detalle de las observaciones, pudiera ser probable, que alguno de ellos reuniera el síndrome de cianosis crónica, dísnea, eritremia y esclerosis pulmonar, conocido en la literatura hispano-americana como "Enfermedad de Ayerza", (Cardiacos negros) porque en una conferencia dada en su clínica, por el Profesor de la Universidad Nacional de Buenos Aires, Dr. Abel Ayerza, en 1901, fué el primero en indicar la entidad clínica de este síndrome morboso; el término "Enfermedad de Ayerza" ya es empleado en la tesis doctoral "La tensión arterial en la tuberculosis pulmonar", 1909, p. 45, del Dr. C. A. Marty de Buenos Aires, al tratar de un grupo especial de enfermos, con tensión arterial de la pulmonar aumentada, hipertrofia del corazón derecho, arterioesclerosis pulmonar y cianosis crónica, descrito ocho años antes por Ayerza, como "cardíacos negros"; posteriormente es usado por Escudero en sus "Conferencias Clínicas" (Buenos Aires) y por el Profesor español García del Real en su "Tratado de Patología Médica", Vol. IV, págs. 405 - 530, 1917.

Barlaro (Revista de la Asoc. Médica Argentina, XXVI, 1917), publica un caso de "Enf. de Ayerza", caracterizado por cianosis, asma, dísnea intensa, hipertrofia cardíaca, eritremia, hepatomegalia, bazo no palpable, Wassermann fuertemente positivo y arterioesclerosis pulmonar y discute su diagnóstico diferencial con la enfermedad de Vaquez, sospechando que muchos casos tales como el primero descripto por el mismo Vaquez, el de Parkes, Weber y Wat-

SON, VAQUEZ y LAUBREY, SAUNDBY y RUSSELL, OSLER (enfisema sin esplenomegalia), y HERRINGHAM, serían en realidad de enfermedad de Ayerza; cree BARLARO que cianosis y dísnea, no se relacionan con la policitemia primaria y si existen asociados, la explicación está en las condiciones de la arteria pulmonar, que caracterizan la enfermedad de Ayerza; su observación era de un sifilítico, pero piensa que acaso no todos sean de lúes o secundarios a una lesión parenquimatosa y teniendo en cuenta cierta analogía con la enfermedad de Raynaud, atribuye a esta la causa de algunos casos de enfermedad de Ayerza.

La descripción más completa de este síndrome, se encuentra en la tesis doctoral de Buenos Aires "Esclerosis secundaria de la arteria pulmonar, (Cardíacos negros)" de 1913 por F. C. ARRILLAGA, publicando once casos de esclerosis pulmonar, extrema cianosis, dísnea y eritremia, a partir del que examinó AYERZA en 1901; el autor delimita la entidad morbosa, primeramente descrita por AYERZA y caracterizada por los síntomas ya indicados, tos con espectoración mucosa o mucopurulenta, cefalalgia, hemoptisis, vértigos, somnolencia etc.; la evolución de los cardíacos negros se cumple en un espacio de dos a cinco años y los pacientes pueden morir, durmiendo sin edema, después de presentar un ruido de galope en el corazón derecho, o también con degeneración miocárdica temprana y anasarca intenso o de una complicación, siendo la más frecuente la bronconeumonía; el diagnóstico diferencial se fundaría en la sintomatología, tiempo de evolución y ser la cianosis adquirida y no el episodio final de una condición asistólica. La enorme hipertrofia y dilatación del corazón derecho son los signos objetivos más importantes en apoyo de una obstrucción pulmonar. La radiografía facilita el diagnóstico al mostrar una sombra cardíaca alargada y ensanchada, con apex redondo y elevado y ventrículo derecho muy extendido hacia el esternón; sobre el borde izquierdo del corazón, en la base, existe una convexidad debida al apéndice auricular izquierdo y sobre éste la sombra ensanchada de la arteria pulmonar y más alta la de la aorta, normal. Se distingue de la dilatación aguda del corazón por el tiempo de evolución y porque en esta afección, también se dilatan notablemente las venas pulmonares, lo que no ocurre en los cardiacos negros. En lo referente a la etiología admite el autor citado las lesiones de los vasos pulmonares, bronquitis, tuberculosis, adherencias pleurales o cualquier condición que produzca un enfisema final y de otra parte las infecciones lentas como sífilis y paludismo y las intoxicaciones.

CONCLUSIONES

Tenemos la opinión de que el estudio clínico e histopatológico del caso que aquí describimos, le separa del grupo de eritremias de Vaquez, encuadrándole en el síndrome morboso de Ayerza, pues son típicos de éste y en nuestra observación se presentaban, la larga evolución de los trastornos pulmonares y el lento desarrollo de la cianosis, eritremia y síntomas secundarios. La autopsia nos reveló una enorme ateroesclerosis de las arterias pulmonares y el examen microscópico, una sífilis latente. En los comienzos, la radiografía hubiera proporcionado un diagnóstico definitivo, si por entonces, alguien hubiera conocido la enfermedad de Ayerza, al punto de poder interpretar correctamente los hallazgos radiográficos; en los archivos se conserva un bosquejo a lápiz de la sombra, que se consideró como de un tumor mediastínico y que se asemeja a la radiografía de la figura novena de la monografía de Arrillaga.

Está fuera de discusión que la eritremia en la enfermedad de Ayerza es secundaria y compensatoria, determinándose el aumento de la actividad funcional de la médula ósea, para suplir la deficiente oxigenación, debida a la obstrucción de la circulación pulmonar; esto ocurre desde luego en los casos de enfermedad de Vaquez con cianosis y disnea y quizá en todos los demás asimismo; cuando concomitantes síntomas están presentes es que la eritremia es secundaria; tampoco es esencial en el síndrome la esplenomegalia, si no secundaria y su aparición puede ser temprana o tardía, según las variables condiciones de la congestión y el aumento de la función esplénica; en casos de lesiones congénitas del septo cardíaco, que se han publicado, se dán en el más alto grado, eritremia, cianosis e hiperplasia medular esenciales en la enfermedad de Osler-Vaquez y el mismo complejo puede resultar de otros estados que conducen a deficiencia crónica de oxígeno.

La enfermedad Osler-Vaquez, con cianosis, eritremia y esplenomegalia, es un síndrome de etiología y patología variada y no una entidad mórbida específica; de él, pudiera separarse un grupo que une a aquellos síntomas la ateroesclerosis de las arterias pulmonares y posee formas clínicas bien diferenciadas, al que será aplicada la denominación de enfermedad de Ayerza y con más propiedad aún "síndrome de Ayerza". El caso que aquí describimos, es el primero de este tipo examinado en Estados Unidos y publicado en el idioma inglés.

Nota adicional

Al preparar nuestro ilustre maestro el Profesor Warthin, su artículo para el "Memorial Osler Volune", actualmente en prensa, le pedimos y él lo aceptó commplacido, que saliera a la luz simultáneamente en alguna revista médica de la República Argentina, patria del insigne Ayerza; de aquí, que lo hayamos traducido al castellano.

Como hemos ayudado a Warthin, revisando la literatura hispano-americana concerniente a la materia, tuvimos ocasión de examinar algunos de los cortes deteniéndonos de preferencia en lo que se refiere al tejido elástico, por estar realizando acerca de éste, un estudio de conjunto en el Laboratorio de Histopatología de la Universidad de Michigan.

Tiñendo con el Weigert secciones de pulmón y de la arteria pulmonar, hemos podido comprobar la analogía de las lesiones microscópicas del elástico, con las ya observadas por los investigadores argentinos y en especial por Arrillaga. El tejido elástico del pulmón, se encuentra notablemente disminuído y aun desaparecido en zonas extensas, quebrado y en fibras sueltas en otras, llegando en ciertos lugares a hacerse imposible el reconocimiento de los alveolos al fallar su armazón elástico.

En el tronco arterial, conservan el paralelismo las fibras de la capa media, si bien en muchos trozos, aparecen interrumpidas y engrosadas; sin embargo, no son tan evidentes las adulteraciones, como en la porción interna de la túnica media, en la llamada capa de Ehlers, entrecortada en muchos puntos, donde el movimiento proliferativo de dentro afuera, invade la elástica de la túnica interna en su totalidad; en esta zona, es muy marcado el clivaje de las fibras elásticas y en algunos sitios existe neoformación de fibrillas, que se tiñen débilmente y que se hace o por dentro, hacia la elástica interna, o entre las mismas fibras de la capa, o entre ella y la externa. Las fibras elásticas de aquella capa, se separan considerablemente, entrecruzándose con absoluta irregularidad.

El proceso de la elástica es análogo en la túnica interna no habiendo homogeneidad en la capa y quedando en ocasiones entre ella y la media, o entre ella y el lúmen, notables espacios que ocupa la neoformación. Las fibras de la elástica interna, son más onduladas, en algunos lugares cortas y gruesas, con neoformación de fibrillas de escasa afinidad tintórea y pueden estar separadas transversalmente por producciones patológicas; la membrana interna, no es tal membrana, apareciendo deshilachada e invadida por el proceso de esclerosis.

En las arterias intrapulmonares las lesiones son semejantes; enorme aumento de la elástica, irregularidad en su disposición, exagerada ondulación de las fibras más internas que limitan el lúmen y clivaje marcado en todas ellas.

Ann Arbor, 1919.

A CASE OF SYPHILIS OF THE PROSTATE

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A CASE OF SYPHILIS OF THE PROSTATE

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IN 1918, a survey of the literature of prostatic syphilis was made by Thompson[1]. He could find only 24 cases of supposed syphilis of the prostate recorded, and of these he accepts only 12 as authentic. The diagnosis in these 12 cases was made upon purely clinical grounds alone, with the exception of one case (Observation XIX, Warthin, 1918) in which the diagnosis was based upon the occurrence of characteristic tissue changes associated with the presence of typical spirochetes of syphilis. This is, therefore, the only positively demonstrated case of syphilis of the prostate existing in the literature at the present time, the writer in a thorough search having failed to add any other. Inasmuch as Thompson's abstract of this case consisted only of a brief quotation from the Harvey Lecture on "The New Pathology of Syphilis"[2], in which the main features of the case were barely mentioned it would seem advisable, because of the importance of the case, to present it with more complete details. That this is justified is shown further by the great interest taken in the case, as evidenced by many inquiries received concerning it. The present report is therefore, made solely to place it on record in a complete form.

CLINICAL HISTORY

Young white male, said to be 19 years of age, fell or jumped from a moving street-car striking squarely upon his head on the pavement. He was taken in an unconscious condition to the University hospital and admitted to Dr. de Nancrède's clinic, March 22, 1917. While being prepared for operation he died. Autopsy ordered by Coroner. The only facts of importance brought out concerning the previous history of the deceased was that he had acquired syphilis some two years previous and had been under recent treatment with mercury and iodides for some time.

GROSS PATHOLOGY

Young male body of large build, 183 cm. long, bones heavy. Appeared older than reported age of 19. Over left shin, on right side of chest, and on left side of head numerous scars of healed syphilitic lesions. Fresh abrasion of right knee. Hematoma of left side of head extending down into neck. No fracture of skull cap. Meninges unusually adherent and thickened. Intrameningeal hemorrhage over right frontal lobe. Larger clot over the left parietal and occipital regions. At base of brain a large blood-clot extending to the posterior border of the foramen magnum. In the floor of the skull a T-shaped fracture beginning to the right of the midline posteriorly to the foramen and extending to the left, across the groove of the left lateral sinus where it met the cross of the T, one branch extending 8 cm. to the left, the other 6 cm. to the right across the floor of skull. Left middle ear was filled with blood. Multiple hemorrhages were found throughout the brain substance.

Main incision showed no pathologic conditions, except a persistent thymus.

Examination of heart and lungs revealed no gross pathologic changes, save a sclerotic patch on the anterior surface of right ventricle.

Spleen was large; very soft; follicles large.

Liver much enlarged, five finger-breadths below edge of ribs in the right nipple line. Capsule smooth except in region of gall bladder. Nothing notable on section. There were many adhesions between the gall bladder, pylorus, colon and duodenum. No stones in gall bladder. Adrenals smaller than normal. Kidneys were of normal size, and presented no abnormalities on section. Other organs also negative. The retroperitoneal lymph nodes were hyperplastic.

The prostate was of normal size and appearance, and on section presented to the eye no pathologic changes. The testes on section appeared to be normal.

MICROSCOPIC PATHOLOGY

Evidences of active syphilis were found in the meninges, lungs, liver, adrenals, prostate and testes, in the form of diffuse or circumscribed plasma-cell infiltrations, often perivascular, with proliferation of blood vessels and fibroblastic tissue, often appearing as miliary vascular granulomas (gummas), showing no caseation, and with oc-

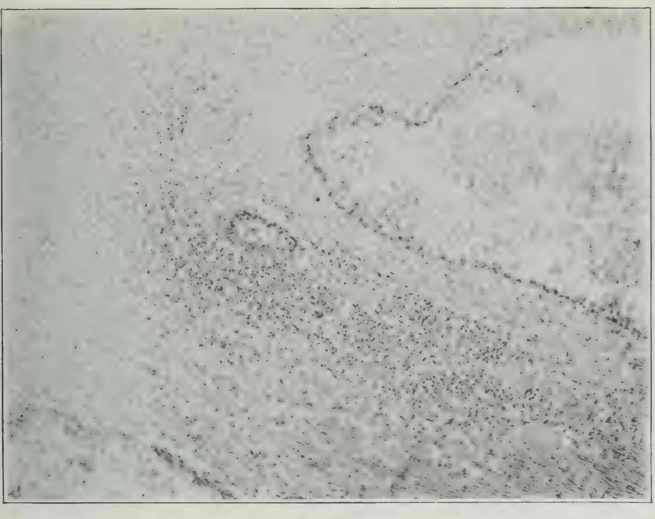

Fig. 1.—Syphilis of the prostate. Plasma-cell infiltrations of stroma, along the smaller vessels.

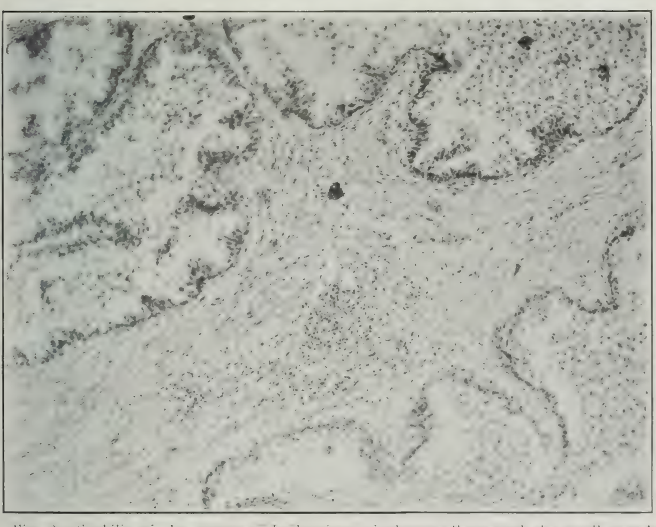

Fig. 2.—Syphilis of the prostate. Infiltrations of plasma-cells around the small vessels in the stroma. These infiltrations are characteristic in that they are not subepithelial as in chronic prostatitis of different etiology.

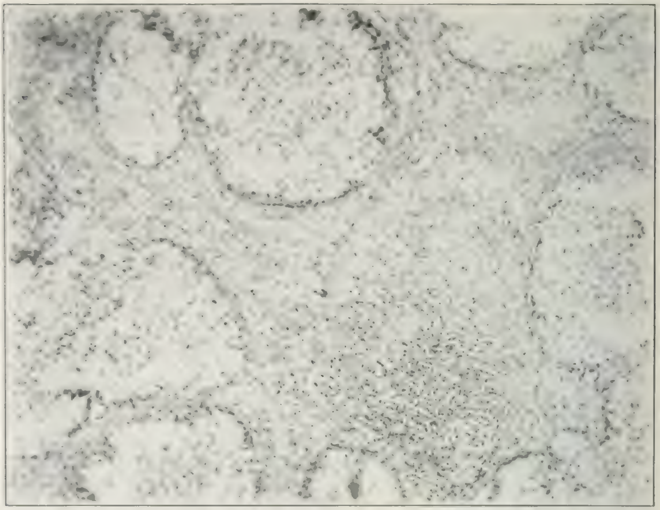

Fig. [illegible]—Syphilis of the prostate. Plasma-cell infiltrations of the stroma.

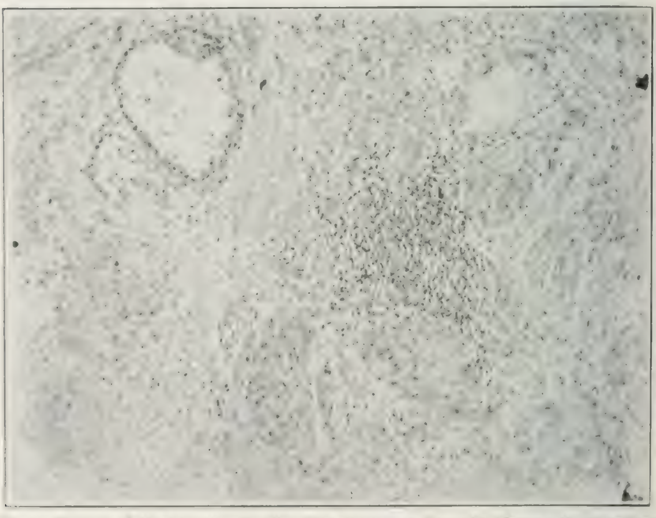

Fig. [illegible]—Syphilis of the prostate. Small miliary gummas, perivascular plasma-cell infiltrations, in prostatic muscle-bundles.

casional giant cells. No tubercles were found in lungs, bronchial nodes or elsewhere. All lymph nodes were hyperplastic; the thymus showed abundant thymic structures; the spleen showed hyperplasia of stroma and lymphoid tissue with exhaustion of the follicles. The adrenals were hypoplastic. The testes showed an interstitial orchitis, with thickening of the basement membrane, plasma cell infiltrations and diminished spermatogenesis, some areas presenting a more advanced picture of syphilitic orchitis.

Multiple hemorrhages were found throughout the brain and in the meninges.

The prostate showed no glandular hyperplasia; the glandular spaces, on the contrary, seemed smaller and less numerous than in the adult prostate, the stroma being greatly in excess. Throughout the stroma there were plasma-cell infiltrations, either diffuse or more circumscribed. These infiltrations followed the capillaries or small veins, and the larger ones were distinctly perivascular, around groups of newly-formed blood vessels, and associated with a definite fibroblastic proliferation of the stroma, with occasional formation of giant cells of the foreign body type. These larger infiltrations and vascular proliferations appeared as miliary granulomas, of the type histologically of miliary gummas. No tendency to caseation was shown; on the contrary, some of the lesions showed thickening and obliteration of the blood vessels with resulting fibrosis. A striking feature of the plasma-cell infiltrations lay in the fact that they do not occur in close relationship to the gland spaces as in other forms of prostatitis, particularly the gonorrheal. The infiltrations are more diffuse and irregular, lie chiefly about half-way between the glands, are distinctly perivascular and not subepithelial. The cells are plasma cells rather than lymphocytes and are not aggregated into germ-centers, as is so frequently the case in chronic gonorrheal prostatitis. They are further characterized by a tendency to new formation of capillaries and an increase of the stroma. In general the prostatic lesions are precisely similar to those produced by syphilis in other organs, (heart, aorta, adrenals, pancreas, etc.). They are remarkable in this case for their degree and extent. They represent a more active process than those of an older latent syphilis.

In these active lesions small groups of typical Spirochete pallida were demonstrated by the Levaditi method. There is, therefore, no doubt that they are syphilitic in nature, and their occurrence in this case demonstrates that the prostate may show the same involvement in syphilis that has been demonstrated for so many other organs and tissues of the body. They differ in no wise from the lesions found in the liver, adrenals and testes of the same case.

This case presents a much earlier stage of syphilis than is usually found at autopsy, and in a younger body, the stage of infection probably dating two years from the initial lesion. It is interesting to note that in this case the heart and aorta showed no syphilitic changes, while the liver, adrenals, prostate and testes showed the greater degree of involvement. The meningeal changes, the hyperplasia of the spleen and lymph nodes, and the pulmonary lesions are probably also the result of the syphilitic infection; although the individual was undoubtedly of the lymphatic type of constitution. The adrenal hypoplasia is to be taken as an evidence of the latter condition.

Although microscopically the prostate showed this picture of extensive infiltrations throughout the stroma, it presented no gross changes, and was of average normal size. That there could have been any clinical symptoms of prostatic involvement seems more than doubtful. The patient had made no complaint of any symptoms connected with his sexual tract, and was known to be actively sexually immoral. His antisyphilitic treatment had apparently been directed against the cutaneous lesions alone. As far as the prostatic lesions are concerned they constitute purely an accidental finding in a routine autopsy examination.

Whether such lesions in the prostate are common in the earlier active stages of syphilis we cannot say until some one makes systematic search for them. As to the prostates of older, more latent, cases of syphilis the occurrence of lesions so marked and so distinctively syphilitic in character as these has not fallen within the range of my experience, although I have examined the prostates of several hundred of such cases. The poverty of the literature speaks the same for other observers. Nevertheless, prostatic hyperplasia and fibrosis occur very frequently in such cases, but without any microscopic changes so characteristic of syphilis as in this young man. Small lymphocyte and plasma-cell infiltrations occur in some of the older cases, with localized areas of sclerotic, small, and apparently new-formed, vessels. It remains to be shown that these have anything to do with the coincident syphilis, or are a part of an associated chronic prostatitis due to other infection. The latter condition re-

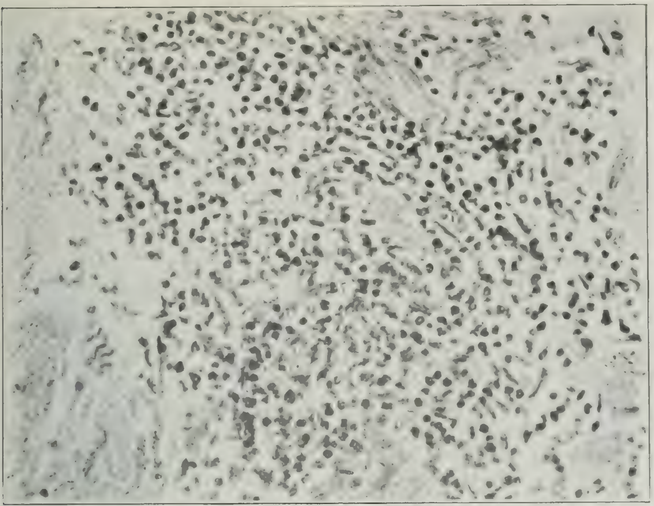

Fig. 5.—Syphilis of the prostate. High power view of small miliary gumma seen in Fig. 4. Plasma-cell infiltrations around new-formed capillaries.

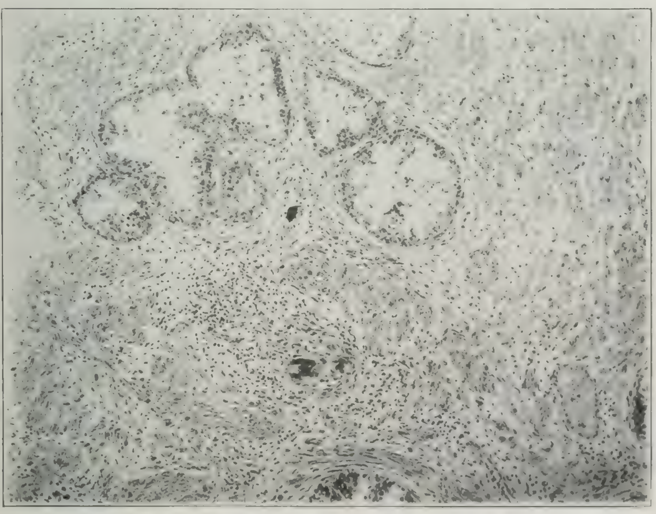

Fig. 6.—Syphilis of the prostate. Small miliary gumma with giant-cells. Spirochaete pallida was found in sections from this.

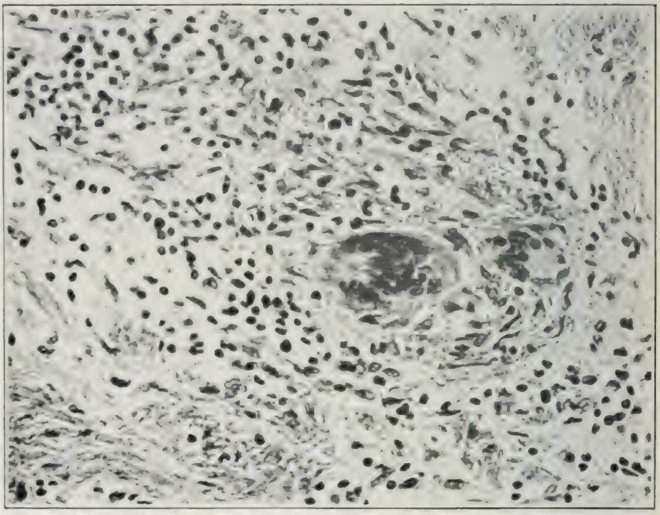

Fig. 7.—High-power view of miliary gumma shown in Fig. 6. Plasma-cells, giant-cells, fibroblastic and angioblastic proliferation.

veals itself in the subepithelial infiltrations of plasma cells and lymphocytes, and in the hyperplasia of the primitive lymph nodes. I have examined the prostates of only a few cases of old syphilis for spirochetes, and the few attempts were unsuccessful. As far as the histologic picture of latent syphilis of the prostate is concerned it is certainly less easily recognized in this organ than in others, but this may be due to its being covered up or complicated with changes due to chronic prostatitis of other etiology. Gumma of the prostate must be extremely rare as compared with that of other organs, else it would have been recognized by this time. It is therefore, possible that the prostate may possess a relatively higher immunity to spirochete localization and growth than other organs, and that the lesions heal sooner than in other tissues. It remains for future investigation to decide this question.

This first positively demonstrated case of syphilis of the prostate shows that the prostate may present characteristic lesions of syphilis relatively early in the course of the infection, and that these may exist in a marked degree without causing any enlargement of the organ, or any symptoms directly referable to it. The histologic picture of syphilis in this organ is identical with that found in the myocardium, aortic wall, adrenals, and other organs.

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RESEARCHES ON SPIROCHAETA PALLIDA

By ALDRED SCOTT WARTHIN

AS A GRADUATE of the literary class of 1888, I consider it, indeed, a very great honor to be chosen to represent the medical alumni of my Alma Mater, on this occasion, the Centennial of Indiana University. In his very gracious introduction, Dr. Wynn has offered an explanation of my scientific work, in that he has discovered that I am a nature lover and fond of the high mountains. But how could anyone come out of Indiana and not be so? I owe three very distinct influences upon my life and work to the circumstances of having been born in Indiana, graduated from a high school in a small country town of Indiana, and of having attended Indiana University. In the county in which I was born and passed the early period of my life three distinct geologic ages stood on edge across its surface, revealing themselves in all the banks and cliffs of the creeks and river valleys. The records of the life of past ages in the form of fossils were everywhere; even the very slabs of the village pavements exhibited the remains of corals, cephalopods, and crinoids to the interested eyes of the young Hoosier schoolboys of that day. Alas, that such potent stimuli to early scientific interest and research should now be replaced by uninspiring cement! But the old stone slabs did excite us to the collecting of fossils and to the desire to find out the meaning of the strangely interesting things we dug from bank and cliff or gathered from the gravel of the streams. Actually, I believe that there is not a stream bed in Decatur county, Indiana, that, as a boy, in the tremendously exciting adventure of collecting, I did not measure, for the greater part of its course, upon hands and knees. To this potent influence of the natural environment, there was added in the high school period the inspiration of a wonderfully gifted "born teacher" of the natural sciences. May I take here the opportunity of paying tribute to the memory of William P. Shannon, a Hoosier schoolmaster, obscure, and unknown to scientific literature or fame, but possessing in a most notable measure the divine fire of scientific enthusiasm and the art of inspiring others to the same appreciation of the wonders of the world of nature. Could any member of his high school classes ever lose from his life the effect produced, when the teacher standing upon an outcrop of the Lower Silurian bade them look across the bed of the shallow sea of the Upper Silurian to the coral reefs of the Devonian, and pictured for them the conditions of those earlier ages! It was such an influence that led me to Indiana University in the early days of President Jordan's career there, and of the first faculty chosen by him. In many ways it was a very primitive University, indeed, but it was also unique in its atmosphere of intellectual freedom, and its insistence upon scientific methods and the worth of the sciences in an education. Can it be only thirty-five years ago that the warfare between the classics and the sciences was being so bitterly waged? Was it only so short a time ago that the family pastor urged against my going to the State University on the ground that it had a faculty of *infidels*!

There can be no doubt that the resuscitation of Indiana University by Dr. Jordan, and the ideals of intellectual liberty for which he and the majority of his colleagues stood marked a new era in American education. To those working with him the outside world became the greater University, exercising infinitely greater influence upon us than the confines of the classroom and the textbook. Again I crept along rocky ledges and the banks of streams, explored underground caves, collected and studied the fauna and flora of Monroe and Brown county woods and hills in the passionate pursuit of a knowledge of life and the world inhabited by it. Much more of an education did I receive from those woods and hills than from the curriculum itself. And so to Indiana and to Indiana University I wish to give thanks for the part they have played in my education. For the passion yet remains of seeing things minutely, of caring for finest details, of comparing and contrasting, of discovering likeness and difference, of knowing things fully, and endeavoring to add some new fact to the sum of knowledge already acquired by the race. And this has led me in the years of my own scientific activities to the pursuit of the knowledge and the investigation of disease and the causes of disease. It may seem a far cry from the woods and limestone ledges of Indiana to the interstices and crannies of the organs and tissues of the human body, but the adventure has been the same.

I consider it a very great honor to be asked at this time to give you a resumé of my researches in the pathology of one of the most important diseases afflicting mankind, syphilis, the "Captain of the Band of Death", as Osler put it. For five centuries no other disease has been so well known to the medical profession in its clinical aspects as has syphilis. Its insidious and often latent course, its relationship to disease of the bones, liver, and central nervous system, and its very frequent manifestation in various forms of skin affections, as well as its congenital transmission thru one or more generations, its apparent incurability,—all of these facts have long been recognized. The great European pathologists and clinicians of the latter half of the nineteenth century express their appreciation of the importance of the disease in such aphorisms as "syphilis, the most protean of all diseases", "Know syphilis, and you know all medicine", or "Syphilis is ninety per cent of all dermatology, and fifty per cent of all internal medicine."

Nevertheless, in spite of such appreciations of the importance of this disease from the most experienced masters of medicine, syphilis has been and remains to this day to the average practitioner a *dermatologic* affection. Its tremendous importance in internal medicine has not been, and even today is not, generally recognized, because of the fact that the early manifestations of syphilis, the chancre and the various syphilides, are chiefly cutaneous, the disease has come to be thought of as dermatologic, and its diagnosis and treatment to be the concern of the dermatologist. Only the syphilitic affections of the central nervous system have been conceded as lying legitimately outside of the field of dermatology. The internist, especially, has been very slow to realize the fact that non-dermatologic syphilis forms a very large part of his material, and that syphilis is often masquerading in the form of the heart, vascular, hepatic, or other organic disturbances presenting themselves to him. He frequently has suspected this, but in the absence of positive etiologic and pathologic proof has not in the past been able to justify his suspicions.

Even the pathologist up to within the last fifteen years has suspected many pathologic conditions to be syphilitic without being able to prove positively that they were. The etiologic agent was unknown, his pathologic criteria for the positive histologic recognition of syphilis were limited to the caseating vascular granuloma, known as *gumma* or *syphiloma*, that since 1874 has been practically the sole lesion accepted by pathologists in general as syphilitic in nature. Without the presence of a definitely gummatous lesion no pathologist dared to make a positive pathologic diagnosis of syphilis, however strong his convictions might be that certain non-gummatous conditions, such as arteriosclerosis, aortic aneurysm, hepatic cirrhosis, orchitis fibrosa, tabes, paresis, leucoderma, leucoplakia, and other conditions frequently associated with the recognized lesion of syphilis, or with a definite clinical history of syphilitic infection might be actual syphilis, or the results in some way of this disease. In explanation of the relationship to syphilis of these non-gummatous conditions, both clinician and pathologist were forced to the hypotheses of "*postsyphilitic*", "*metasyphilitic*", and "*parasyphilitic*" processes—conditions bearing a certain relationship to syphilis, but which were not this disease, nor even necessarily caused by it.

Up to the last decade our knowledge of the pathologic lesions of syphilis has been limited to the conception of the gumma, and the pathology of syphilis, as given in our textbooks today, is essentially based upon the occurrence of this type of granuloma. As late as the Harvey Lecture in 1915, Fordyce says: "Aside from gummatous involvement of the viscera little is known of the effects of the infection on the various organs." Gummata, however, are relatively rare, particularly in certain organs and tissues, and this is the explanation of the fact that the recognized pathology of syphilis has never been able to correlate itself with either the clinician's or the pathologist's suspicion of a much greater incidence and importance to be ascribed to syphilis than the frequency of occurrence of the gumma would indicate.

Only with the discovery of the etiologic agent of syphilis, in 1905, did it become possible for us to make progress in our knowledge of this disease. My own clinical and pathologic studies in Vienna during the nineties had convinced me of the tremendous importance of syphilis. As other pathologists had done, I also had noted the association of aortic aneurysm and arteriosclerosis with cases of known syphilis, and with tabes and paresis. In addition I was struck by a similar association in the case of fibroid myocarditis, chronic interstitial pancreatitis, fibroid orchitis, and slight localized inflammatory changes of a very chronic character in many organs and tissues. These I suspected to be syphilitic in nature, but could not prove it.

With the announcement of the discovery of *Spirochaeta pallida* by Schaudinn, in 1905, and the corroboration by the other investigators, during the following year, of the association of this organism with syphilitic lesions, I at once, in 1906, began a series of investigations that have occupied me largely during a period of almost fifteen years. It is the result of this long period of investigation that I am now intending to present to you in a very condensed form, aided by a series of lantern slides that will, I think, speak more clearly and forcibly than any verbal description can possibly do.

My first investigations were concerned with congenital syphilis of the heart. In a series of cases of congenital syphilitic infection I was able to demonstrate conclusively the fact that the heart is one of the chief organs involved in congenital syphilis, that *Spirochaeta pallida* occurs in great numbers in the myocardium, often without causing any recognizable changes in the heart muscle, in other cases associated with focal fatty degeneration, atrophy, or necrosis of the muscle, while other cases still show a definite form of myocarditis due to the presence of the spirochaetes. This form of myocarditis had been noted once only in the literature as possibly syphilitic in character, and this supposition I was able to confirm with certainty by the demonstration of the constant presence of the spirochaete in this form of tissue lesion. This type of myocarditis is characterized by diffuse infiltrations of lymphocytes and plasma-cells, fibroblasts and angioblasts, with a relatively slight new-formation of stroma or reticular tissue, often semifluid or mucoid in character, giving mucin-staining reactions. These lesions occur in the intermuscular spaces, along the smallest vascular branches; less frequently do they develop around the larger coronary branches. They occur also in the endocardium and in the pericardium; congenital syphilitic endocarditis and pericarditis are realities. The myocardial changes vary in degree, from very slight proliferation of the interstitial cells to larger infiltrations that may take on the character of gummata. Caseation is, however, very rare. Associated with this type of myocarditis there occur rarely myxoma-like masses of the same type of cells replacing the heart muscle, and containing large colonies of spirochaetes. In the interstitial form the spirochaetes occur in great numbers, either diffusely or localized in the infiltrations; any portion of the heart wall may be involved. The number of the spirochaetes, however, bears no definite relation to the severity of the reaction.

A fortunate series of autopsy cases of congenital syphilis in older children, adolescents, and young adults threw further light upon the nature of myocardial syphilis and its relation to fibroid heart. Progressive and permanent damage to the heart muscle, with resulting fibrosis and cardiac insufficiency, were found to follow directly upon the type of myocarditis described above. Active lesions and healed ones were found existing in the same heart, even in cases as old as twenty-one years. In congenital cardiac syphilis the lesions are more widely scattered than in the adult myocardium, the right ventricular wall being as often involved as the left. Fibrosis is the ultimate sequela.

Other features of congenital syphilis were also studied with reference to the localization of the spirochaetes and the associated lesions, particularly in the case of the liver, spleen, pancreas, and placenta. The same type of pathologic lesion as in the myocardium was found to be the rule; gummatous lesions were the rare exceptions. It was demonstrated beyond any doubt that the essential lesion produced in congenital infections by the *Spirochaeta pallida* was of the nature of a mild interstitial or productive inflammation, leading ultimately to fibrosis and diminished function. It must, however, again be emphasized that in congenital syphilis the spirochaetes may occur in various tissues in enormous numbers without the production of any changes in the tissue-elements recognizable by any of our methods of examination, thus indicating a high degree of commensal adaptation.

From the study of congenital cardiac syphilis it was a natural step to the study of myocardial changes in acquired syphilis. My autopsy material gave me abundant opportunity for this. The hearts of cases of known syphilis were first studied, particularly those of aortic aneurysm, tabes, paresis, and other forms of chronic syphilis. The histologic study was carried along parallel with the search for the spirochaete by means of the Levaditi silver-impregnation method. In every case of known syphilitic infection characteristic lesions were found in the myocardium, in the form of slight, or more marked, infiltrations of lymphocytes and plasma cells between the muscle fibres. These infiltrations are diffuse or patchy; very rarely are they focal or sharply circumscribed. Miliary infiltrations occasionally occur, but larger caseating gummata of the myocardium are very rare. In the great majority of cases the infiltrations are of very slight degree, the cells being arranged in close single file between the fibres. To the inexperienced observer there may seem to be only a slight increase of the interstitial nuclei. Polymorphonuclears rarely occur in these infiltrations, and eosinophiles are not present. The cells of the infiltration are probably chiefly histiogenetic and endothelial lymphocytes and young formative cells derived from the stroma. Larger epithelioid fibroblasts are also very common in the healing areas. There is an increase of the reticular fibres; in the earlier and more active areas fluid spaces occur between the fibres, and in these a staining-reaction for mucin is often obtained. Evidences of a progressive healing and fibrosis are always present in the chronic cases. In older healed areas the stroma becomes fibroid and hyaline. The fibroid heart is the ultimate outcome of these interstitial lesions. The heart-muscle fibres are apparently very resistant to the infection, but as the stroma increases and becomes fibroid, and with the obliteration of the capillaries, the muscle becomes atrophic and many of the fibres disappear, so that the cicatricial areas increase in size.

The myocardial lesions in acquired syphilis are found chiefly in the wall of the left ventricle, in the anterior portion of the wall just above the apex, the adjacent portion of the septum, and less often in the posterior wall of the left ventricle near the mitral ring. The infiltrations are found more frequently near the endocardium than toward the epicardium as in congenital syphilis. These lesions are in the great majority of cases microscopic, and may be found in marked degree, even when there are no gross changes in the heart. In other cases dilatations, hypertrophy, atrophy, and fibroid patches in the wall of the left ventricle are apparent in the gross examination. Thrombosis of the left ventricle, aneurysmal dilatation of the anterior wall just above the apex, and rupture of the heart occur as sequelae of syphilitic myocarditis. I have seen over thirty cases of thrombosis of the left ventricle in which the thrombus was attached directly over an area of syphilitic disease in the ventricular wall.

In the myocardial lesions spirochaetes of syphilis have been demonstrated often enough to convince me that they are due to nothing but the *Spirochaeta pallida*, and that they represent absolutely specific lesions of syphilitic infection. The search for the spirochæte is, however, very difficult and time-consuming in the case of chronic acquired syphilitic infection. The organisms are not numerous, and many blocks and great numbers of sections must often be examined before a group of the spirochaetes may be found. Moreover, the Levaditi method, the most reliable method available during the greater part of the time in which this research was in progress, is very capricious, and so much depends upon freshness of tissue, conditions of fixation, etc., that the method must be regarded as a difficult one, even in the hands of experts. For this reason, my laboratory has also engaged itself with the problem of improving the technical methods necessary for the demonstration of the spirochaete. My own modification of the Levaditi method has been found to give better and more constant results than the original; but we have recently replaced this method by one much superior, which I shall describe later.

From the study of hearts of known syphilis our studies progressed to the hearts of patients in whom a syphilitic infection had never been recognized or suspected. Such cases appeared in my autopsy material in striking numbers—in about forty per cent of the entire autopsy material. The majority of the patients showing an unrecognized latent syphilis present the clinical picture of the cardio-vascular-renal complex. Their symptoms were those of cardiac incompensation, myocardial insufficiency, hypertrophy or dilatation of the heart, chronic passive congestion, general arteriosclerosis, and frequently renal disease. They died a cardiac death; and the microscopic lesions in these cases were identical with those found in known cases of syphilis, and in them also were found repeatedly typical spirochaetes of syphilis. These cases, therefore, were syphilis—latent infections, unrecognized. In other cases giving history of early infection but supposedly cured and running many years without recognizable signs of syphilis, with negative Wasserman reactions, the same tissue-lesions in the heart, associated with the presence of *Spirochaeta pallida*, were found.

Taking up the aorta in all of these cases, also known cases of syphilis, "cured" and uncured, and unrecognizable clinically, the microscopical examination showed characteristic infiltrations of plasma-cells and lymphocytes along the course of the vasa vasorum thru the adventitia and media, associated with slight or marked atherosclerotic changes. An aorta presenting no pathological changes to the naked eye may show on microscopic examination typical syphilitic infiltrations in media or adventitia. The gross appearances of the aorta cannot be taken as an absolute criterion of the condition of the vessel. Syphilis of the aorta may exist in apparently normal aortas, or in aortas showing the picture of an ordinary atherosclerosis, or when the gross pathologic picture is that of a syphilitic mesaortitis. In these aortic lesions the spirochaetes are found with greater difficulty than in the myocardium. The number is usually small. The more active the process, the more easily found are the organisms. The lesions are found most often in the arch of the aorta and in the abdominal portion. Our work has confirmed the syphilitic nature of aortic aneurysm. I have not seen a single instance of the latter that was not syphilitic. While in congenital syphilis a localization of spirochaetes in the intima of the aorta may occur, I have never noted such in the aorta in acquired syphilis. The atherosclerotic changes in the intima and media appear to be due to a slow anaemic infarction resulting from the obliteration of the arteries of the vasa vasorum. The lymphocytic and plasma-cell infiltrations are in the early stages most marked in and around the walls of the small arterioles; later these become obliterated by a concentric proliferation of the endothelium, giving the appearance of a small tubercle or gumma.

Similar syphilitic lesions were found in the pulmonary artery and in the wall of an aneurysm of the latter vessel, with demonstration of the spirochaete. The microscopic changes are the same; infiltrations in the adventitia and media, along the vasa vasorum, with obliteration of the latter and the production of atherosclerotic changes in the intima. A similar syphilitic mesarteritis of the pulmonary arteries was found also in a case of chronic cyanosis and polycythemia (Vaquez's disease), enabling me to interpret this case as one of "Ayerza's disease", the first one to be reported in this country. It was noted also that sclerotic changes in the pulmonary arteries were not uncommon in the lungs of cases presenting syphilitic lesions in the myocardium and other organs; and that a more or less patchy fibrosis of such lungs was usually coincident.

Extending the study of syphilis of the arteries to the femoral and popliteal arteries and their larger branches, as well as to the walls of aneurysms of these vessels, identical syphilitic lesions with those in the aorta and pulmonary artery were found. In one case the entire systemic arterial trunks and their smaller branches showed the most marked degree of syphilitic inflammation associated with multiple thromboses.

Following the study of syphilis of the blood vessels, the pancreas of all cases showing syphilitic lesions in the myocardium and aorta was carefully studied. In all of the older cases of syphilis the pancreas showed more or less atrophy, with patches of chronic interstitial pancreatitis. In every one of these cases active areas of plasma-cell infiltrations, with stroma increase, were also present. These lesions were identical in kind with the syphilitic lesions of the myocardium and aorta and in two of the cases *Spirochaeta pallida* was demonstrated in the pancreatic lesion. Syphilis of the pancreas had been practically unknown before. It is a most interesting fact that out of twelve cases of diabetes coming to autopsy, only two did not show the presence of syphilitic lesions in the pancreas and other organs. If interstitial pancreatitis leading to fibrosis of the islands of Langerhans is a cause of diabetes, then syphilis being a cause of this condition must be reckoned with in the etiology of diabetes.

In the adrenals of cases showing syphilitic lesions in the heart, aorta, and pancreas, the same small infiltrations of lymphocytes and plasma-cells were found. They occur in the medullary portion or in the inner portion of the reticular zone. In three cases of Addison's disease the syphilitic infiltrations and fibrosis were so marked as to cause nearly complete atrophy of the organ. Syphilitic infiltrations were found also in the semilunar and adrenal ganglia. Another striking feature observed in the adrenals of chronic syphilis was a marked lipoidosis of the cortex.

The liver of all the cases of latent chronic syphilis, as well as in clinically active cases, showed chronic passive congestion and atrophy, while inflammatory lesions, varying from slight infiltrations of the periportal tissues to the most severe forms of cirrhosis, were also constant findings. Ten cases of atrophic cirrhosis, one of the Hanot type, and three of the Glissonian, occurred in this material, in addition to five cases of gumma and eight cases of hepar lobatum. All of these showed characteristic plasma-cell lesions of the same type as in the other organs.

In all male cases of acquired syphilis, active or latent, the testes showed marked lesions in the form of atrophy, fibrosis, and plasma-cell infiltrations. Spermatogenesis was dimished in the mildest cases, and in older, more severe infections the entire organ may be fibroid. The interstitial cells remain preserved, and often appear hypertrophic, even in cases in which the patients had complained of a premature loss of sexual desire. It is evident that the testes are especially affected by the syphilitic infection. In congenital syphilis enormous numbers of spirochaetes may be found in this organ without any perceptible histologic changes; but in the older cases the spirochaetes occur only in the active areas of infiltration. A seminal transmission in old and latent syphilis seems very probable.

It is impossible, in the time allotted me here, to take up each individual organ and tissue in detail. It must suffice to say, that in the brain and spinal cord, in the spinal nerves and ganglia, in the prevertebral tissues, root of mesentery, along the branches of the portal vein, in the pelvic tissues, in the lungs, and elsewhere, there constantly are found in the bodies of old syphilitics minute perivascular infiltrations of lymphocytes and plasma-cells, associated with fibroblastic and angioblastic proliferations, leading to obliteration of the vessels, and eventually to fibrosis. Only in the spleen, kidneys, ovary, and uterus have such typical lesions of latent syphilis not been found; but it must also be stated that no especial study has as yet been made of these organs.

The results of these researches are very important; in fact, they have been said to be epoch-making in so far as the history of syphilis is concerned. They show that the gumma is not the essential pathological lesion of syphilis, but that it is, on the contrary, a relatively rare formation. The great majority of cases of syphilitic infection run their course without the formation of gummatous granulomas.

The essential pathology of late or latent acquired syphilis is the occurrence of a chronic irritative or inflammatory process, characterized by lymphocytic and plasma-cell infiltrations in the stroma about the blood-vessels and lymphatics, with slight angioblastic and fibroblastic proliferations, leading eventually to fibrosis and atrophy of the parenchyma, with corresponding loss of function. In the active lesions relatively avirulent spirochaetes are found in small numbers; these disappear as fibrosis develops.

The syphilitic becomes a "spirochaete carrier", the host of an organism symbiotic in a high degree. In this respect it is to be classed with the trypanosome, organisms of malaria, the bacilli of leprosy and tuberculosis, the pyogenic cocci, and perhaps even more commensal organisms, as the colon bacillus, etc.

Syphilis is a generalized process from the very beginning most probably. The spirochaetes spread thruout the entire body, and colonize particularly in the interstitial tissues, around the smallest blood-vessels, especially in the nervous system, myocardium, aorta, liver, pancreas, adrenals, and testes. Wherever they produce irritation, the characteristic inflammatory infiltrations are found. In individual cases especial predilection for one system, organ, or tissue may be shown; but there is, as yet, no explanation of such predilections. The infection is a steadily progressive one. Healing areas and active ones occur side by side, and in the old cases the evidence of extensive healing is found in the occurrence of widespread fibrosis. I have, however, seen no case histologically "cured"; in every one examined active syphilitic areas were still present. "Cured" syphilis is latent syphilis, and the carrying of the spirochaete produces an immunity against new infection with this organism. The price paid for this immunity is the slowly progressive defensive inflammatory infiltration, which after many years results in fibrosis and atrophy, with a corresponding diminution of function, asserting itself clinically as myocarditis, aortitis, aneurysm, hepatitis, diabetes, tabes, or paresis, or in other milder forms of functional disturbance.

Mild for many years, the syphilitic infection may at any time rise violently above the clinical horizon in more virulent form, and with a more rapidly progressive course. What lies at the bottom of this increase in virulence or lowering of tissue-resistance we do not yet know. The individual affected with syphilis has always this sword hanging over his head. It may fall at any time, or it may never fall; but his expectancy of life is lowered, and he is most likely to die a premature death from affections not ordinarily recognized as syphilis. Particularly does he die a myocardial death My work has shown that death in the middle years of life is in an extraordinary degree the result of latent syphilis—the result of a long period of a mild infection with a highly symbiotic organism producing slight injuries, until the sum total of such injury causes functional disturbances leading eventually to death.

This work throws also much light on the question of the incidence of syphilis in our population It is undoubtedly much greater than is usually supposed. Latent syphilis undoubtedly lies at the bottom of many conditions not suspected of being syphilis, either because the patient gives no history or sign of having ever had a chancre or skin lesions, or having had these, is regarded as absolutely cured. Undoubtedly many cases are innocent infections, many congenital, and many acquired without any recognition of the earlier stages and without any diagnosis until years after.

My work has shown further that the ultimate diagnosis of syphilis is a microscopic one, resting upon the microscopic determination of specific tissue-lesions caused by the *Spirochaeta pallida.* The etiologic agent of the disease being known, and the characteristic lesions produced by it now demonstrated by this work, the importance of syphilis in producing internal affections and disorders has been made clear, and the *Spirochaeta pallida* receives consequently an increased pathogenic value. More than ever is syphilis the "Captain of the Band of Death"!

In solving the etiologic problem of so many internal disorders, the way to prevention and therapeutic management is also indicated. The individual infected with syphilis usually receives an intensive treatment for a limited period, after which he is discharged as "cured". If he is a "spirochaete carrier" with certain possibilities of danger to him because of that fact, the damage resulting from the latent infection may be reduced to a minimum, by careful attention to general hygiene and an avoidance of all conditions tending to lower the general resistance of the body. A periodic antisyphilitic treatment may also serve to keep the infection from becoming more virulent at any time.

Since the diagnosis of syphilis depends upon the demonstration of the spirochaete in the tissue-lesions it becomes very necessary to obtain a method by which this can be carried out as quickly and easily as possible. Levaditi's silver-impregnation method has been the only method available. This has, however, required ten to fourteen days, and the tissue is impregnated in mass, so that histological control is difficult, as it cannot be applied to single sections. Moreover, the results obtained by this method are very uneven and uncertain. In connection with Mr. A. C. Starry, the writer has evolved two methods, by which silver-impregnation is carried out in single sections mounted on cover-glasses, cut from paraffin-embedded formol-fixed tissue. Ordinary diagnostic blocks can be used. With the second of these methods, our agar-silver method, preparations of spirochaetes can be obtained within one hour after cutting the sections and mounting them on cover-glasses. We have found this method, moreover, to be much more certain of good results than the original Levaditi, and have obtained spirochaetes by its use in tissues in which the original Levaditi absolutely failed. We consider this method a great technical advance in the demonstration and study of *Spirochaeta pallida* in the tissues.

In closing, the researches outlined above create a new pathology for an ancient disease, and thereby, a new clinical attitude and an altered therapeutic conception. The aphorisms of the older physicians have been confirmed, the suspicions of the older pathologists justified, and syphilis stands today revealed in truth as the Great Killer of mankind.

THE UNIVERSITY MEDICAL SCHOOL AND THE STATE[1]

By ALDRED SCOTT WARTHIN

THE SPEAKER preceding me has spoken of state medicine. I wish to go a step farther than he has done and to say a few words for *university* state medicine or *state university* medicine, as you may choose to interpret it.

The great social ferment of the times, following upon the upheaval of the Great War, does not leave medicine untouched. The profession of the art and science of healing, in its origin an institution of social service, but developing, thru the exigencies of modern civilization, more and more into a business vocation in which large financial rewards are possible to the successful practitioner, does not today escape the charge of commercialism. Assertions are made, that, in spite of all the social service medicine still renders thru the medium of charitable institutions, a large per cent of the working population does not, or cannot, have efficient medical treatment or adequate protection from disease. The laborer does not want charity, but only the very rich can obtain the most highly skilled medical service. Based upon these claims arises the cry for a further socialization or nationalization of the practice of medicine, in the form of "compulsory health insurance", "state medicine", "communal medicine", and the like.

The strength and significance of this movement cannot be doubted, and the medical profession cannot ignore it. In this country the Association for Labor Legislation has for several years conducted a vigorous campaign for compulsory health insurance, and its program has received the approval and vigorous support of the majority of the labor organizations, as well as of other societies or associations less directly connected with labor. It has become a plank in a political platform. In eight states commissions have been appointed for the consideration of a health insurance program, and in two states actual health insurance bills have already been introduced. In England, the National Insurance Act was passed without adequate consultation of the medical profession upon whom the burden of carrying this law into effect was thrown; and again in 1919, the income limit, within which insurance in England was made obligatory, was extended, with certain exceptions, from £160 to £250, without consulting the practitioners at all. In the report of the Local Government Board for 1917–18, it was shown that of the 24,000 registered practitioners of England and Wales, over 16,000 were engaged in insurance domiciliary practice, while the great majority of the others were associated with some kind of communal medical service. We may well ask, what further extensions may be demanded, and granted? Shall compulsory health insurance be extended to all classes of citizens? Shall all medical work be placed upon a communal basis, with the practitioner acting as the full-time salaried servant of the community? A few medical men support this latter program with enthusiasm; but from the reports of committees in the American Medical Association and many local medical societies, the majority of American practitioners would reject it as undemocratic, destructive to initiative, freedom of action, and the personal relation, so important in the practice of medicine.

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[1] Response to toast at a dinner given at the Claypool Hotel, Indianapolis, May 5, 1920, for the guests and the medical faculty of the University.

But that some form of communal medicine is inevitable, there can be no doubt. In fact, it is already here. The greatest function of the state is the preservation of the life, liberty, and happiness of all its citizens; and this means the preservation of the *health* of its citizens It is to the self-interest of the state to keep its citizens well. Upon this line the state has already proceeded far, in its development of preventive medicine, thru the communal mechanisms of state and local departments of health Public safety against the epidemic contagious diseases was primarily sought, but state medicine has been extended to occupational diseases, industrial hygiene, child labor, protection of water supplies, disposal of sewage and garbage, street cleaning, medical and dental inspection of school children, mothers' pensions, educational campaigns against the fly, mosquito, tuberculosis, and the venereal diseases, and along a hundred other lines of preventive medicine. The state also assumes to take care of its insane and mentally incompetent, and in some degree of its indigent sick, in some form of charity at least. In the full development of its function in the prevention of disease the state health department has developed the diagnostic laboratory, by which means bacteriologic, serologic, toxicologic, and even pathologic examinations are furnished free, or at cost. The most important and productive field of medicine, today, and to many minds, the most attractive, is that of preventive medicine, rather than curative.

The advances in state preventive medicine have been very notable in the more advanced states of the Union, altho much yet remains to be accomplished in this field of state medicine. The division of the state into communal health districts, according to population, with the establishment of local laboratories and health centers, as provided in the bills introduced in several of the states, will place state preventive medicine on a still higher plane of efficiency. The question, however, that we must now face is the enlargement of the field of state medicine from its present one of the prevention of disease to that of the diagnosis and treatment of disease. Shall the state invade the field of the practice of medicine?

That some form of state diagnostic and curative medicine is coming is inevitable. It may be found necessary as the final development of preventive medicine; or it may come as the only solution of our medical social problems. Indeed, as far as the first necessity is concerned, the state has already undertaken curative measures in the case of rabies, malaria, hookworm infection, tuberculosis, and the venereal diseases, as well as affections of the eyes, nose, and teeth, and orthopedic conditions. If the necessity claimed, of insufficient and inadequate medical service for the laboring classes, actually exists, then either compulsory health insurance or some other form of state medicine must be developed to give them the medical help they should have. The majority of the American medical profession apparently regard compulsory health insurance as non-American, undemocratic, and destructive of personal initiative and liberty; but to an alternative plan of state medicine by which the state can offer to those who need it, at rates within their means, efficient diagnostic and medical services from skilled, or event expert, laboratory men, physicians, and surgeons, there seems to be but little opposition. Such medical services should be elective, and not obligatory. A mechanism by which such a state medicine can be accomplished has already been touched upon by the previous speaker, in the form of health centers, scattered thruout the state, according to density of population, each center to have attached to it a hospital for the diagnosis and treatment of disease, with a staff of full or part-time salaried laboratory and clinical experts, who will give an equal service to all who ask treatment, the compensation for such services being determined by the income or earning-power of the patient. But many practical problems present themselves, as to the means of financing and the control of such communal hospitals. The evils of political patronage, apparently so inseparable from our state health services, could create infinite damage if introduced into medical practice. What more dangerous union could be imagined than that of politics and communal medical service!

This brings me to the chief point I wish to make; and that is, in the event of the adoption of any form of state medicine of the kind just described, the control of such local hospitals should be under the state university medical school, their policies directed by it, and the standard of service and the fitness of the medical appointees determined by the ideals of medical education inculcated by that institution. Why should not the state, thru its university school of medicine, enter the field of medical practice, and give to all of the citizens of the state who desire it the service of the best men in medicine it can enlist in its faculty? Where should the best medical men in the state be but on that faculty? A state hospital, or several, or many state hospitals, under the control of the university medical school, would seem the ideal way of developing a really efficient form of state medicine. A central hospital at the school itself, with local branches developed to meet the needs of different communities, a body of full-time salaried laboratory and clinical men of the highest type, chosen on university criteria, possessing teaching and research qualities and the desire for social service, giving equal service to all who apply, and a compensation determined by income or earning-power—all of this seems a practical and sane form of state medicine. I believe that this is a feasible plan and that it would result in a highly efficient system of state medicine. It would pay its own way.

Progress has already been made in some of the states towards such a system. If I may be permitted to point out what a sister state, Michigan, has already accomplished, you will realize the advanced position she is holding in state medicine today. However, the beginnings were not primarily altruistic. With a medical school located in a small university town, it became necessary in the earlier years of the school's development to obtain clinical material for the instruction of the medical students. Fortunately for the university, and for the state, various efforts to remove the medical school to the neighboring city of Detroit have never been permitted to succeed, and the school remains at Ann Arbor, where it has developed for itself adequate clinics for instruction with an abundance of clinical material, and, incidentally has furnished a striking example of *university state medicine.* The evolution has been a most interesting one. The university hospital is not, and has never been a charity hospital; it has but a few free beds, and these have not been furnished by the state. It has offered its services—those of a well-trained group of teaching clinicians—at a low or moderate cost—to the citizens of the state, who had not the means to pay the regular charges for such services, or who were sent for consultation to the hospital by any practitioner of the state. As a concession to the profession of the state, the university hospital was not made available to the well-to-do or the rich of Michigan, except as the physician of such patients desired to send them there for aid in diagnosis or treatment. In addition to the service rendered the poorer citizens of the state, the hospital thus became used as a consulting center. As the service rendered to the state came gradually to be appreciated by the citizens, various bills were passed by the state legislature, with the effect not only of increasing the clinical material available for instruction, but also of emphasizing the hospital's social service to the state. One of these public acts, passed in 1913, provided for the medical and surgical treatment at the university hospital of any child deformed, or afflicted with a malady that can be remedied, and whose parents are unable to provide proper treatment, such child to be sent to the hospital thru the probate judge of the county, the expenses of such treatment to be audited by the auditor-general, and paid by the state to the university. In 1915, another act provided free hospital service, and medical and surgical treatment to any adult legal resident of any county who can be benefited, and who is unable to pay for such care and treatment, as well as for the care of any pregnant woman unable to pay, and for the children of such during the period of hospital care, under a similar probate court jurisdiction, and payment of the hospital expenses by the state or county.

The result of the social service thus rendered to the state of Michigan by its university hospital has been a greatly increased appreciation of this service by the citizens, and a growing tendency toward a further development of this form of state medicine. The hospital facilities becoming inadequate, the last legislature was asked for a new and adequate building, the entire cost to be extended over a number of years in divided grants. In place of the smaller sum asked for, an immediate grant of one million dollars was voluntarily offered and given, the sentiment in the legislature being for an extension of the services rendered by the hospital. In the history of state university requests and legislative grants, when did the like occur before? Such an event certainly marks a new era.

One form of state medicine—the state university hospital—has, therefore, shown itself practical and worthy. It has won the confidence of the citizens of the state to such an extent that it is now entering upon a new stage of progress. The two chief clinical departments, medicine and surgery, have been put upon a full-time basis, with salaried clinicians working for the hospital alone. The rich, as well as the poor, are to be treated equally, the compensation to be adjusted to ability to pay; the hospital, itself, is to become commercial to the extent of paying its way from the income received. This stage of development is still experimental; the outcome will be watched with great interest by all other medical schools, particularly those of the state universities. Iowa has already followed Michigan to the extent of copying the laws above mentioned, furnishing clinical material to the state university hospital. Upon the success of Michigan's new venture will depend the action of other schools. It is evident that new problems are involved in the new scheme. Under the old plan of half-time clinicians engaged also in private practice, the private hospital grew up for the accommodation of the well-to-do excluded by law from the state hospital, but who desired the services of the same body of clinicians. Under the new system these parasitic institutions must pass away. Will the old commercialism, however, be replaced by another form, even more dangerous to medical teaching and research than the divided interests of the old situation? In any scheme contemplating a division of profits such a danger is a very real one; but with a fixed salary basis it could not exist. Undoubtedly the right men for this work are those who would welcome a fixed adequate salary, with the added opportunities for teaching and research.

In closing, some form of state medicine seems inevitable. I believe that the safest form would be, what I have attempted to outline above, a system of state hospitals, or a hospital, controlled by what should be the most enlightened body of medical men in the state—the faculty of the state university medical school—in other words, a state university medicine. What Michigan has accomplished in this direction is also possible for Indiana University and your Medical School. Such an institution in Indiana will do what it has done for the University of Michigan, it will bring the citizens of the state into a closer relation with the University, it will make them more sympathetic with its needs, lessen opposition to increased taxation and greater budgets, and make for greater understanding and appreciation of all the functions of the University.

The Incidence and Histopathology of Tuberculosis of the Tonsils

BASED ON EIGHT THOUSAND SIX HUNDRED TONSILLECTOMIES

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Based on Eight Thousand Six Hundred Tonsillectomies

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THE INCIDENCE AND HISTOPATHOLOGY OF TUBERCULOSIS OF THE TONSILS

BASED ON EIGHT THOUSAND SIX HUNDRED TONSILLECTOMIES.*

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An unusual opportunity to study the less common pathologic changes in the tonsil has been afforded in the department of pathology of the University of Michigan through the practice of making routine histologic examinations of all tonsils received from the University Hospitals. This material now represents approximately 9,000 cases. This is a far larger series than has been reported from the standpoint of a microscopic study hitherto, and lends itself to quantitative analysis with the prospect of yielding much more accurate results, within the limitations of the data considered, than the smaller numbers forming the basis of previous studies.

While tuberculosis occurs in but a small percentage of the tonsils examined, as compared to the various chronic inflammatory manifestations, hyperplasias and metaplasias, which are present in varying degrees in all tonsils, regardless of the clinical history, its occurence is of sufficient frequence to constitute one of the chief reasons for continuing the labor involved in the routine histological examination of all tonsils received. It greatly outranks the other chronic infective granulomas; recognizable syphilitic lesions being next in order, but by no means as frequent, while actinomycosis of the tonsil ranks third in this group, although met with only very rarely.

This paper deals with two aspects of tonsil tuberculosis. First, (a) the total incidence will be considered, with the effect on the incidence of the character of the population from which the cases are drawn; (b) the incidence in various age groups, and (c) the incidence as to sex. In the second part of the paper, the histopathology of tuberculosis of the tonsil will be discussed and the cases separated into a limited number of groups showing lesions of quite different character in each group and having an entirely different clinical significance in each instance.

LITERATURE

A complete survey of the literature is unnecessary at the present time, but reference will be made to all important articles in their proper connection and a rather extensive bibliography is appended.

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* From the Department of Pathology, University of Michigan.

The literature of tuberculosis of the tonsils is of comparatively recent date. This is due, in part, to Virchow's (1864) statement, quoted in most of the older textbooks, to the effect that tuberculosis of the tonsil had not yet been observed. Much more important in this connection, however, is the fact that, in its most common forms, tuberculosis of the tonsil cannot be diagnosed macroscopically, and, therefore, becomes the subject of report only as histologic examinations are more frequently made. The earliest observations seem to be those of Cornil[1] (1875), (Quoted by Friedmann[2]) who found an ulcerating lesion of the pharynx and tonsil in an otherwise healthy appearing individual; of Deplous[3] (1878), who found a tuberculous ulceration of the tonsil as well as of the adjacent parts in a child dying of pulmonary tuberculosis, and of Orth[4] who produced tonsil tuberculosis experimentally in dogs in the course of a series of feeding experiments with tuberculous tissues, apparently a primary focus.

Numerous articles have dealt with the occurrence of tonsil tuberculosis in necropsy material derived from patients dying with obvious tuberculosis lesions elsewhere in the body. Some of the more important of these are the papers of Strassmann,[5] Dmochowski,[6] Schlenker,[7] Kruckmann,[8] Walsham,[9] Labbé and Lévi-Sirugue[10] and Friedmann. The frequency of secondary tonsil involvement in cases of advanced pulmonary tuberculosis was thus early established. The earliest reference to well authenticated cases of primary tuberculosis of the tonsil is that of Orth[11] who found characteristic microscopic lesions in the tonsils of children dying from diphtheria without evidence of tuberculosis elsewhere in the body.

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[1] Cornil: Quoted by Friedmann.[2]

[2] Friedmann, F. F.: Ueber die Bedeutung der Gaumentonsillen von jungen Kindern als Eingangspforte für die tuberkulöse Infection, Beitr. z. path. Anat. **28**:66, 1900.

[3] Quoted by Friedmann.[2]

[4] Orth, J.: Experimentelle Untersuchungen über Fütterungstuberculose, Arch. f. path. Anat. u. Physiol. **76**:216, 1879.

[5] Strassmann, F.: Ueber Tuberculose der Tonsillen, Arch. f. path. Anat. u. Physiol. **96**:319, 1884.

[6] Dmochowski: Ueber secundäre Erkrankungen der Mandeln und der Balgdrüsen an der Zungenwurzel bei Schwindsüchtigen, Beitr. z. path. Anat. **10**:481, 1891.

[7] Schlenker, E.: Beiträge zur Lehre von der menschlichen Tuberculose, Arch. f. path. Anat. u. Physiol. **134**:161, 1893.

[8] Krückmann, E.: Ueber die Beziehungen der Tuberculose der Halslymphdrüsen zu der Tonsillen, Arch. f. path. Anat. **138**:534, 1894.

[9] Walsham: Latent Tuberculosis of the Tonsil, Tr. Path. Soc. Lond. **49**: 67, 1898.

[10] Labbé and Lévi-Sirugue: Etude sur les lésions de l'amygdale dans quelques cas de tuberculose, Bull. Soc. Anat. de Par., 6 Serie **1**:919, 1899.

[11] Orth: Lehrbuch der speciellen pathologischen Anatomie, 1887, p. 663.

The work of Lermoyez[12] drew attention to tuberculosis of the pharyngeal tonsils, and the papers of Pluder and Fischer,[13] McBride and Turner,[14] Brieger,[15] Piffl,[16] Rethi[17] and Hynitzsche,[18] among others, resulted. The occurrence of tonsil tuberculosis during childhood has been investigated especially by Latham,[19] Friedmann,[2] Ito,[20] Kingsford[21] and Mitchell.[22]

Of the important contributions dealing in a general way with the subject of tonsil tuberculosis, or with special phases of it, such as the tonsil as a point of entrance of infection; the nature of the infecting organism, whether bovine or human; relationship to lymphoid hyperplasia and relationship to cervical gland and pulmonary tuberculosis, the papers of Gottstein,[23] Grober,[24] Bandelier,[25] Carmichael,[26] Sewall,[27] Mitchell,[28] and of Crowe, Watkins and Rothholz[29] are especially worthy of mention.

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[12] Lermoyez, M.: Les végétations adénoides tuberculeuses, Presse méd. **3**:413, 1895.

[13] Pluder and Fischer: Ueber primäre latente Tuberculose der Rachenmandelhyperplasie, Arch. f. Laryngol. u. Rhinol. **4**:372, 1896.

[14] McBride and Turner: Nasopharyngeal Adenoids, Edinburgh M. J. **43**: 355, 471, 598, 1897.

[15] Brieger: Ueber die Beziehungen der Rachenmandelhyperplasie zur Tuberculose, Ztschr. f. Ohrenheilk. **33**:191, 1898.

[16] Piffl: Hyperplasie und Tuberculose der Rachenmandel, Ztschr. f. Heilk. **20**:297, 1899.

[17] Rethi: Die latente Tuberculose der Rachenmandel, Wien. klin. Rundschau **14**:509, 1900.

[18] Hynitsche: Anatomic Investigations on the Hypertrophy of the Pharyngeal Tonsil, Arch. of Otol. **29**:356, 1900.

[19] Latham, A.: Pulmonary Tuberculosis in Early Childhood, Lancet **2**: 1785, 1900.

[20] Ito: Untersuchungen über die im Rachen befindlichen Eingangspforten der Tuberkulose, Berl. klin. Wchnschr. **40**:27, 1903.

[21] Kingsford, L.: Tuberculosis of the Tonsils in Children, Lancet **1**:89, 1904.

[22] Mitchell, A. P.: Primary Tuberculosis of the Faucial Tonsils in Children, J. Pathol. & Bacteriol. **21**:248, 1917. Also J. Laryngol., Rhinol. & Otol. **33**:8, 40, 1918.

[23] Gottstein, G.: Pharynx- und Gaumentonsille primäre Eingangspforten der Tuberculose, Berl. klin. Wchnschr. **33**:689, 714, 1896.

[24] Grober, J. A.: Die Infectionswege der Pleura, Deutsch. Arch. f. klin. Med. **58**:296, 1900. Die Tonsillen als Eintrittspforten für Krankheitserreger besonders für den Tuberkelbazillus, Klin. Jahrb. **14**:547, 1905.

[25] Bandelier: Die Tonsillen als Eingangspforten der Tuberkelbazillen Beitr. z. Klin. der Tuberk. **6**:1, 1906.

[26] Carmichael, E. S.: Tuberculosis of the Tonsil, Associated with Tuberculous Glands of the Neck, Proc. Roy. Soc. Med., Sect. Dis. Child., London **3**:27, 1910.

[27] Sewall, E. C.: Histologic Examination of the Faucial Tonsils with Reference to Tuberculosis, J. A. M. A. **46**:867 (March 25) 1911.

[28] Mitchell, A. P.: The Infection of Children with the Bovine Tubercle Bacillus, Brit. M. J. **1**:125, 1914.

[29] Crowe, Watkins and Rothholz: Relation of Tonsillar and Nasopharyngeal Infections to General Systemic Disorders, Bull. Johns Hopkins Hosp. **28**:1, 1917.

MATERIAL.

The material used in this analysis consists of the faucial and pharyngeal tonsils from 8,697 consecutive cases, operated on in the University Hospitals and submitted to the pathologic laboratory of the University of Michigan for routine histologic examination. The period of time represented covers the years from 1906 to 1919, inclusive, but by far the greater part of the material has been received during the past five years. It may be stated roughly that the 8,697 cases indicate the examination of 8,697 pairs of faucial tonsils and of about one-fourth as many pharyngeal tonsils. While this is not strictly true, the instances in which only one faucial tonsil was removed or the pharyngeal tonsil alone was submitted for examination are so few that it makes no appreciable difference in the statistical analyses presented here, whether they are included or not.

The patients from whom these tonsils were removed were selected cases only to the extent that they all exhibited one or more of the conditions which have been accepted by many otolaryngologists during the past few years as indicating need for tonsillectomy. As a group, they are much more nearly representative of the total population of the region from which they came than is usually the case in similar studies. This is due to the peculiar character of the University Hospital which is in no sense a local clinic but draws its patients from the entire state and neighboring states as well. All ages, from one year to 78 years, are represented, the rural as well as the urban fraction of the population, and the extremes of social standing. Two groups of patients, however, have been sufficiently numerous to influence the curve of incidence of tuberculosis to an extent which will require further consideration in its proper place. These are the inmates of the state institutions for dependent and defective children, who at one time were brought almost en masse to the University Hospitals to have their tonsils removed; and university students, many of whom submit to tonsillectomy while resident in Ann Arbor. It may be noted here that this second group, coming for the greater part from comfortable middle class homes, has enjoyed living conditions free from those institutional risks to which the first has been subjected. Attention must also be called to the fact that in the last few years an increasing number of middle-aged patients have been referred to the otolaryngologist for tonsillectomy from other clinical departments. This, also, has had its influence upon the incidence of tonsillar tuberculosis.

METHOD

Immediately on removal, the tonsils were placed in a 10 per cent. solution of liquor formaldehydi and, after adequate fixation, portions were selected for microscopic examination. As a rule, all of the fragments of the pharyngeal tonsil were embedded. The faucial tonsils were bisected in a vertical plane at right angles to the mucous surface, and from the cut face of one of the halves thus obtained the sections for microscopic examination were made. The other half was marked by attaching a numbered tag by means of a drop of thick gum acacia solution and dropped into a jar of alcohol for preservation in case it should be necessary to refer to it again. Usual methods of paraffin infiltration and embedding, and hematoxylin and eosin staining, were routinely employed, with the additional use of various special stains when indicated.

As a rule, only one or two sections were examined from each block, but care was taken to cover each section systematically in order that every field might be scrutinized. The blocks of adenoid tissue were sliced away until the largest possible sections could be obtained, and the half tonsils were embedded to cut from the entire flat surface, again giving the largest possible sections as well as those which would intersect the ramifications of the greatest number of crypts. A few sections, thus carefully oriented and systematically searched, will yield a higher percentage of positive results than serial sections of limited portions of the tonsil, for although tonsil tuberculosis is very often a local process involving only a small fraction of the entire organ, it is also very frequently a crypt infection, as will be pointed out later, hence it is important to examine some portion of each crypt as far as possible. We believe that our method accomplishes these purposes as satisfactorily as is possible with a limited number of sections.

The results, however, as expressed by the curve of incidence, represent minimal figures, for there can be no doubt that if it were possible to examine each tonsil throughout in serial sections taken at an interval of 0.1 mm. or less, the total number of cases would be increased by the addition of those in which single tubercles or small groups of tubercles would be found in the anterior and posterior peripheral portions of the tonsil. Sewall [27] and his associates attempted to estimate the percentage of error thus introduced by making serial sections of tonsils previously diagnosed as nontuberculous after the examination of a few sections. They found one case positive in the first series of twenty pairs examined and none in another series of twenty-three pairs, or 2.3 per cent. altogether. The percentage in 772 pairs examined by the original method was 3.9, which would seem to indicate that about 38 per cent. of the cases had been missed at first through incomplete examination. It is exceedingly dangerous, however, to assume from so occasional an occurrence as once in forty-three cases that the same ratio would hold throughout. Moreover, the original examination was made by a few frozen sections and there are no tissues in which diagnosis from frozen sections is more difficult than those of the lymph-adenoid group. It is quite unlikely that the sections examined in the first instance would anywhere nearly approximate in size those obtained from the entire cut surface of a longitudinally bisected hyperplastic tonsil.

The method used here is the only one suitable for the routine examination of a large material, and there can be no doubt that the results are more accurate than those obtained from any other single method, except the examination of serial sections of the entire tonsil. The staining of direct smears from the cut surface yields of necessity but a very occasional positive result. It may, however, give false positives because of the occasional presence of tubercle bacilli in the tonsillar crypts without invasion of the tonsil itself. The examination of sections stained for tubercle bacilli is exceedingly laborious, requiring, oftentimes, the prolonged search of many sections, even when the tissue lesions are abundant. This method is of considerable value in confirming the histologic diagnosis in doubtful cases, but the results afforded by it can be accepted only when positive. Its limitations have been explained as due to the small number, or rapid disintegration, of the bacilli. It must also be borne in mind that after certain routine fixations, as, for instance, formol, staining of tubercle bacilli in sections is rendered either very difficult or impossible. The cultivation of the bacilli is a difficult procedure because of the prevalence of contaminating organisms and as a rule only a small portion of each tonsil can be employed in this method. Von Scheibner's[30] earlier results were all negative in a small series of twenty cases. Mitchell[28] seems to have attained a fair measure of success in his use of egg medium.

Animal inoculation has been much exploited as a method of investigation of tonsil tuberculosis since the report of Dieulafoy,[31] leading to his controversy with Cornil[32] as to the availability of this procedure. It is open to several serious objections; death of experimental animals from septic processes, false positives from surface organisms and those in the crypts, the small amount of tonsillar tissue which can be used, the failure to inoculate a sufficient number of organisms to overcome the resistance of the animal and the length of time necessary before the result can be ascertained. Special procedures have been devised to overcome some of these objections. Mitchell[22] employed a 2 per cent. aqueous solution of ericolin to effect a partial sterilization of the tonsil according to the method of Twort. Latham[19] used only the more central portions of the tonsil for inoculation. Von Scheibner[30] washed

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30. Von Scheibner: Bilden die Tonsillen häufige Eingangspforten für die Tuberkelbacillen? Beitr. z. path. Anat. **26**:511, 1899. Also Deutsch. med. Wchnschr. **25**:343, 1899.

31. Dieulafoy: Tuberculose larvée des trois amygdales, Bull. de l'Acad de méd., Par. **33**:437, 1895.

32. Cornil: Sur la tuberculose larvée de trois amygdales, La Semaine méd. **15**:[illegible] 1895.

the tonsils in a dilute sublimate solution. The most elaborate method of all, that of Austin,[33] makes use of antiformin digestion and concentration of the minced and ground tonsil tissue, followed by injection into a traumatized inguinal lymph node of a guinea-pig. He found, however, but one positive in forty-five consecutive cases, contrasting with fifteen positive cases out of ninety-six as reported by Dieulafoy [31] in his use of this method without its later refinements. Even in the one case of Austin one might well question the results since the positive finding was obtained in only one guinea-pig which might have been previously infected with tuberculosis.

Against the purely histopathologic method of diagnosis of tonsil tuberculosis, the chief objection has been the supposed possibility of mistaking for tubercles the pseudotubercles resulting from the presence of mechanical foreign bodies or from organisms other than the bacillus tuberculosis. But as Sewall [27] points out, there is no more reason for questioning the etiology of a histological tubercle in the tonsil than in the lung, liver or spleen, in which situations diagnoses made from sections alone are constantly being accepted. We cannot, however, agree with him as to the relative infrequency of the foreign body pseudotubercle in the tonsil as indicated by his statement that in 1,544 tonsils examined not one "foreign body giant cell" was found. On the contrary, such giant cells occur with surprising frequency, but in them the provocative foreign body is usually to be found as a minute spicule, fiber or slender bristle, serving in itself to differentiate the cell as a true foreign body giant cell which, with whatever epithelioid or fibroblastic proliferation may accompany it, constitutes a foreign body pseudotubercle (Figs. 1 and 2). The difference in refraction and the lack of staining usually render such foreign bodies very easy of detection. The calcareous deposits rarely occurring in the giant cells of true tubercles must be borne in mind in this connection lest one fall into the opposite error. These concentric masses of lime salt, apparently first described by Gottstein,[23] are very striking when they occur in large numbers, and in no degree discredit a diagnosis of tuberculosis.

A possible source of error is found in the superficial resemblance between a confluent noncaseating tuberculosis and an active diffuse syphilis of the tonsil. The differential diagnosis depends on the relatively avascular character of the former and the arrangement of the epithelioid cells in whorls about minute capillaries in the latter. In confirmation of the diagnosis, specific staining for the organism may be carried out. In our experience, the demonstration of the spirochete in the tonsil is attended with less difficulty than the demonstration of the tubercle bacillus.

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[33] Austin, R. S.: Bacillus Tuberculosis in the Tonsils of Children Clinically Nontuberculous, Am. J. Dis. Child. **18**:15 (July) 1919.

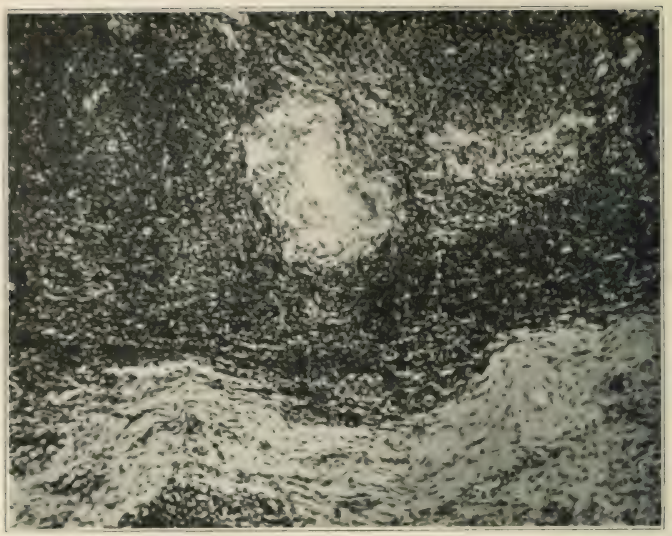

Fig. 1.—Photomicrograph of a foreign body pseudotubercle in the tonsil. The foreign body shows several fine parallel striae, as if composed of a bundle of fibrils, probably vegetable material, and is surrounded by foreign body giant cells. Hemalum and eosin stain, Zeiss "B" objective, without ocular.

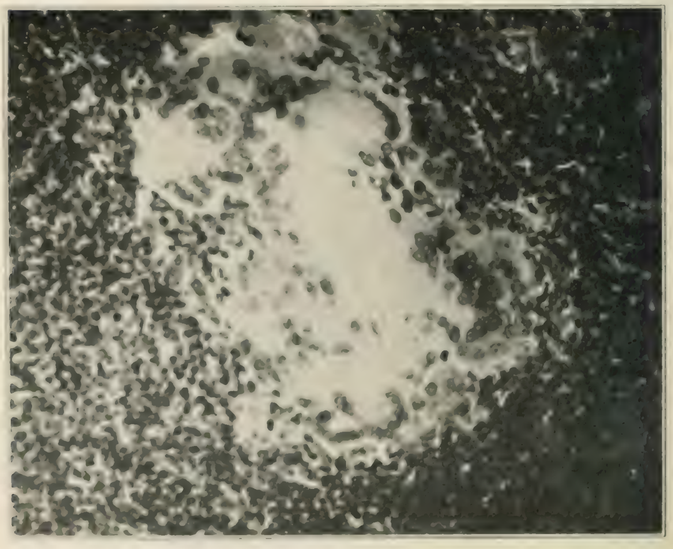

Fig. 2.—Photomicrograph of same foreign body pseudotubercle as in Figure 1. Higher power to show detail of foreign body and giant cells. Zeiss "DD" objective, without ocular.

THE INCIDENCE OF TONSIL TUBERCULOSIS

The histologic examination of the material removed in 8,697 tonsillectomies, including in practically all cases both faucial tonsils and in many cases both faucial tonsils and adenoids, showed active tuberculosis in 204 instances, a case incidence of 2.35 per cent. This falls within the limits established by other reported series. Taking only those reports which include 100 or more cases, unselected in respect to tuberculosis elsewhere in the body, and omitting several dealing with pharyngeal tonsils only, Table 1 may be constructed.

The aggregate of these previous statistical studies gives a case incidence varying only 0.79 per cent. from our own, although the individual results vary over a wide range.

TABLE 1.—Incidence of Tonsil Tuberculosis

Author	Cases	Tuberculous	Per Cent.
Albrechts[34]	1,060	3	0.3
Barnes[36]	150	3	2.0
Crowe, Watkins and Rothholz[29]	1,000	46	4.6
Judd[37]	1,000	23*	2.3
Lewin[38]	200	9	4.5
Robertson[39]	232	19 (?)	8.0
Sewall[27]	772	30	3.9
Willis[40]	108	9	8.0
	4,522	142	3.1

* Usually quoted as given here, but the report is ambiguous as is shown by the following direct quotation: "In our cases we were seldom able to trace back to the source of entrance. Examinations of several hundred tonsils showed tubercles in much less than 1 per cent. In 1,000 cases, 2.3 per cent. had positive tuberculous lesions."

In Table 2 the distribution of the entire series of 8,697 cases as to age, sex and number of positive and negative cases for each sex at each age is presented.

For purposes of comparison, however, and to avoid as far as possible the error of chance occurrence by increasing the size of the groups, these data will be condensed into five year age periods

Of the 8,697 cases, there were 8,343 in which information regarding the sex of the patient was available. Of 4,631 tonsillectomies in male patients, 103, or 2.23 per cent., were found to be tuberculous. In 3,712 female patients the tonsils gave histologic evidence of active

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[34] Albrechts: Quoted by Ravenel.[35]

[35] J. A. M. A. **66**:613 (Feb. 26) 1916.

[36] Barnes, H. A.: The Tonsils, C. V. Mosby, 1914, p. 160.

[37] Judd: Treatment of Tuberculous Glands of the Neck, Ann. Surg. **52**: 758, 1910.

[38] Lewin: Ueber Tuberculose der Rachenmandel, Arch. f. Laryngol. u. Rhinol. **9**:377, 1899.

[39] Robertson, C. M.: Certain Facts Concerning Faucial Tonsils, J. A. M. A. **47**:1725, 1906.

[40] Willis, B. C.: Inflammatory Pathology of the Tonsil, South. M. J. **7**: 747, 1914.

TABLE 2.—Incidence of Tonsil Tuberculosis as to Age and Sex

Age	Males		Females		Sex Not Known		Total		
	Posi-tive	Nega-tive	Posi-tive	Nega-tive	Posi-tive	Nega-tive	Posi-tive	Nega-tive	Total
1	...	6	...	3	...	1	...	10	10
2	[illegible]	31	2	[illegible]	...	....	2	54	56
3	[illegible]	94	[illegible]	[illegible]	...	2	2	151	153
4	...	110	...	68	...	2	...	180	180
5	...	[illegible]	...	[illegible]	...	3	...	262	262
6	[illegible]	[illegible]	[illegible]	[illegible]	...	6	6	289	295
7	...	173	4	136	...	3	4	312	316
8	6	185	4	139	...	4	10	328	338
9	3	152	1	128	...	....	4	280	284
10	2	128	4	109	...	2	6	239	245
11	1	144	3	105	...	3	4	252	256
12	[illegible]	[illegible]	[illegible]	[illegible]	...	4	5	219	224
13	[illegible]	76	...	117	...	1	3	194	197
14	[illegible]	100	[illegible]	106	...	...	6	206	212
15	[illegible]	86	[illegible]	86	...	...	3	172	175
16	3	82	2	89	...	1	5	172	177
17	2	75	6	88	...	....	8	163	171
18	[illegible]	134	[illegible]	116	...	1	9	251	260
19	4	141	5	115	...	2	9	258	267
20	8	[illegible]	3	[illegible]	...	[illegible]	11	313	324
21	4	209	4	124	...	...	8	333	341
22	[illegible]	198	[illegible]	88	...	1	5	287	292
23	[illegible]	139	[illegible]	93	...	1	6	233	239
24	[illegible]	157	4	85	...	2	7	244	251
25	[illegible]	102	...	57	...	....	2	159	161
26	4	97	2	57	...	...	6	154	160
27	1	49	1	56	...	1	2	106	108
28	4	52	1	47	...	2	5	101	106
29	...	38	1	36	...	....	1	74	75
30	3	36	...	47	...	...	3	83	86
31	1	35	...	23	...	...	1	58	59
32	[illegible]	37	[illegible]	34	...	1	3	72	75
33	1	37	...	16	...	....	1	53	54
34	1	29	...	15	...	1	1	45	46
35	1	42	2	27	...	....	3	69	72
36	...	26	...	18	...	....	...	44	44
37	...	16	...	17	...	....	...	33	33
38	...	16	1	15	...	1	1	32	33
39	[illegible]	19	...	8	...	...	2	27	29
40	...	20	1	21	...	....	1	41	42
41	...	8	1	12	...	....	1	20	21
42	...	10	...	15	...	....	...	25	25
43	...	16	...	14	...	....	...	30	30
44	...	4	2	6	...	...	2	10	12
45	...	8	...	9	...	...	...	17	17
46	...	12	...	10	...	...	...	22	22
47	...	4	...	4	...	...	...	8	8
48	...	6	...	14	...	...	...	20	20
49	...	7	...	8	...	...	...	15	15
50	...	5	...	7	...	...	...	12	12
51	1	5	...	3	...	...	1	8	9
52	...	8	...	8	...	...	...	16	16
53	...	4	...	5	...	...	...	9	9
54	...	3	...	3	...	...	...	6	6
55	...	[illegible]	...	[illegible]	...	...	...	8	8
56	...	[illegible]	...	9	...	...	...	14	14
57	...	[illegible]	...	2	...	...	...	5	5
58	1	[illegible]	...	2	...	...	1	4	5
59	...	1	1	1	...	...	1	2	3
60	...	[illegible]	...	[illegible]	...	...	...	5	5
61	...	1	...	1	...	...	...	2	2
62	...	[illegible]	...	1	...	...	...	4	4
63	...	4	...	2	...	...	...	6	6
64	...	[illegible]	...	[illegible]	...	...	...	3	3
65	...	[illegible]	...	1	...	..	...	3	3
[illegible]	...	1	...	...	...	...	...	1	1
[illegible]	...	1	...	...	...	...	...	1	1
70	...	1	...	...	...	...	...	1	1
76	...	...	...	...	...	1	...	1	1
77	...	..	...	1	...	...	...	1	1
78	...	1	...	...	...	...	...	1	1
Not given	22	711	[illegible]	[illegible]	[illegible]	[illegible]	43	1,660	1,703
Totals	[illegible]	[illegible]	[illegible]	2,616	5	[illegible]	204	8,493	8,697

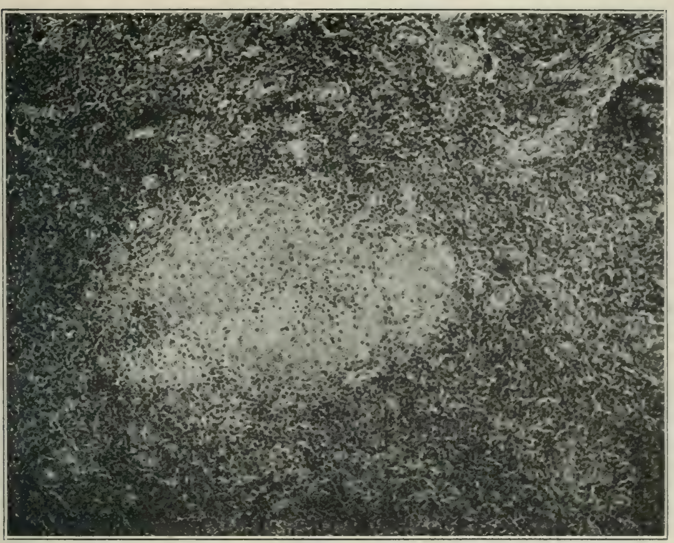

Fig. 3.—Photomicrograph of a tonsil epithelioid tubercle containing a few lymphocytes in its central portion. No caseation. No giant cells. Toluidin blue stain. Zeiss "B" objective, without ocular.

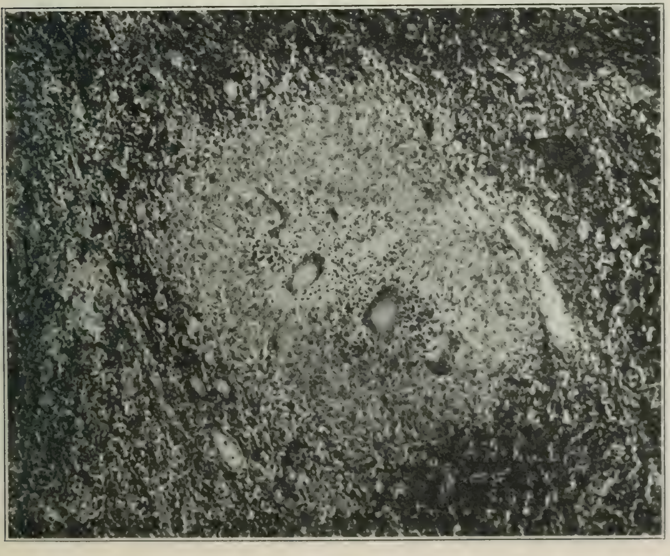

Fig. 4.—Photomicrograph of a tonsil epithelioid, giant cell and lymphocyte tubercle. Very slight caseation. Toluidin blue stain. Zeiss "B" objective, without ocular

tuberculosis in ninety-six instances, or 2.59 per cent. There is, then, very little difference between the sexes in respect to the incidence of tonsil tuberculosis, but the slightly greater prevalence in females has constantly been present throughout the period covered by this investigation. The distribution of the cases of known age according to sex by five year age periods, as presented in Table 3, shows, also, that at practically all ages this greater incidence in females exists. In one period only, ages 26 to 30, is this condition reversed, and in that instance the total number of cases is not so great but that the discrepancy may have the element of chance occurrence as its sole explanation. The somewhat greater incidence in females of all ages seems, at first glance, to be in contradiction to the general experience for tuberculosis as shown by mortality statistics.[41] In the registration area, and for the year 1917, deaths of females from tuberculosis were 9.9 per cent. of the total number of female deaths and deaths of males from tuberculosis were 10.6 per cent. of the total number of male deaths. However, the tonsil cases here considered fall very largely between the ages of 5 and 24 years. Comparing the tuberculosis mortality in these ages with the total mortality of the same period, it is found that female deaths from tuberculosis are 29.2 per cent. of female deaths from all causes and male deaths from tuberculosis 20.9 per cent. of male deaths from all causes. Although it is not altogether safe to substitute mortality statistics for morbidity statistics and to use the number dying at a given age as an index of the number living, it appears, nevertheless, that the greater incidence of tonsillar tuberculosis in females is but part of a general greater incidence of tuberculosis in females during that period of life at which tonsillectomy is most frequently performed.

TABLE 3.—Incidence of Tonsil Tuberculosis as to Five Year Age Periods

Age Periods	Males			Females			Sex-Unknown		Totals		
	Positive	Negative	Per Cent. Positive	Positive	Negative	Per Cent. Positive	Positive	Negative	Positive	Negative	Per Cent. Positive
1 to 5	2	380	0.53	2	269	0.74	..	8	4	657	0.61
6 to 10	14	808	1.70	16	625	2.56	..	15	30	1,448	2.07
11 to 15	10	526	1.87	11	509	2.12	..	8	21	1,043	1.97
16 to 20	21	621	3.27	21	530	3.81	..	6	42	1,157	3.50
21 to 25	13	805	1.58	15	447	3.25	..	4	28	1,266	2.18
26 to 30	12	279	4.15	5	238	2.06	..	3	17	518	3.18
31 to 35	5	170	2.86	4	125	3.10	..	2	9	297	2.94
36 to 40	2	97	2.02	2	79	2.47	..	1	4	177	2.21
Over 40	2	133	1.48	4	146	2.67	..	1	6	280	2.07

The youngest cases of tonsillar tuberculosis were found at 2 years of age, two in number, and the oldest case at 59 years. The age incidence by five year periods is shown in the final column of Table 3. It

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[41] Mortality Statistics, 1917, U. S. Bureau of Census, 1919.

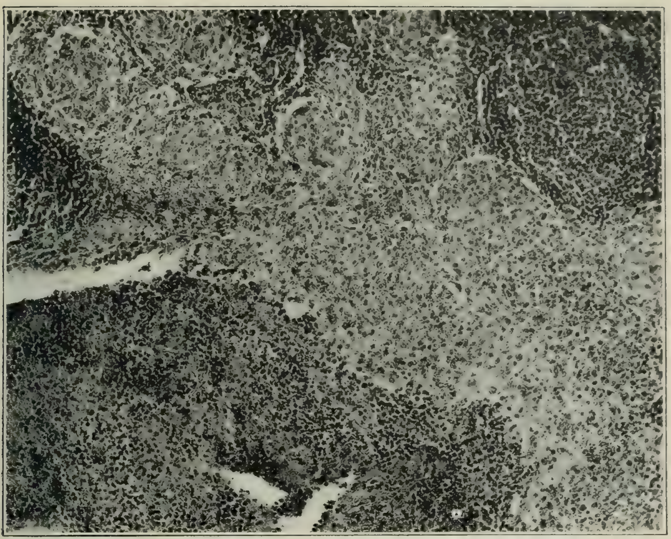

Fig. 5.—Photomicrograph showing confluent epithelioid tubercles beneath the mucosa of a crypt. Lymph follicle uninvolved. Hemalum and eosin stain. Zeiss "B," without ocular. Bellow's length 150 cm.

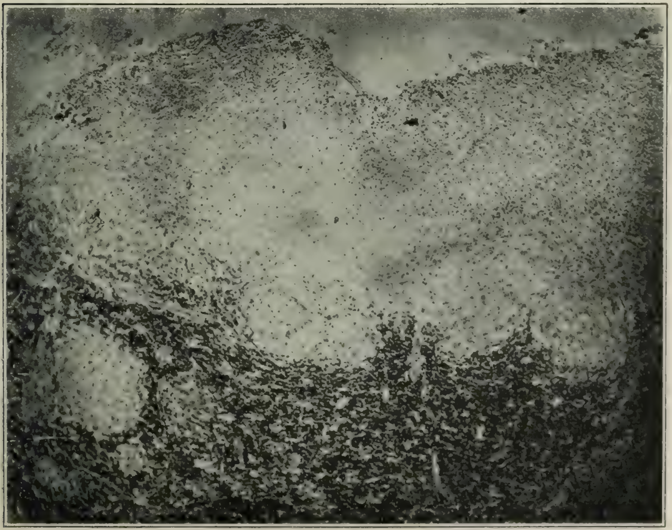

Fig. 6.—Photomicrograph of caseating tuberculous lesion involving the mucosa of a tonsillar crypt. Numerous small epithelioid tubercles beneath the area of caseation. Toluidin blue stain. Zeiss "B," without ocular. Bellow's length 85 cm.

shows an increased incidence after the years of infancy and early childhood have passed. When compared with similar statistics, compiled in 1917 but hitherto unpublished,[42] dealing with this series of cases up to that date, the effect of changes in the constitution of the population considered, is brought out. At that time 4,543 tonsillectomies yielded 138 cases of tuberculosis, a total incidence of slightly over 3 per cent. A comparison of the five year period age incidence at that time with that now obtained is possible in the parallel columns of Table 4. It will be noted that at the time of the earlier compilation the incidence was higher in each age group than at the present time and that this difference was most marked in the very young and in those of adult years. The explanation is probably to be found, in the first place, in the large number of children from certain state institutions who have been sent to the University Hospital for tonsillectomy. The incidence of tonsillar tuberculosis was high in this group (institutional infection) and these patients formed a much greater part of the entire series in the earlier than in the later years of the period considered. In the second place, the material here considered reflects a changing viewpoint on the part of the otolaryngologist in that an increasing number of patients were operated in the later years in the hope of removing a primary chronic purulent focus. These patients are more especially of adult years and in them the incidence of tonsillar tuberculosis is low. The effect of this group has been to lower the incidence after the age of 25, which had been brought to a high level by reason of the fact that in the earlier years tuberculosis of the cervical nodes or of the lungs was, in a greater proportion of cases, the reason for tonsillectomy in those past the age of excessive lymphoid hyperplasia.

TABLE 4.—Five Year Age Period Incidence in 1917 and in 1920

Age Period	Per Cent. Positive in 1917	Per Cent. Positive in 1920
1 to 5	1.4	0.61
6 to 10	2.8	2.07
11 to 15	2.5	1.97
16 to 20	3.9	3.50
21 to 25	2.8	2.18
26 to 30	5.1	3.18
Over 30	5.0	2.46

The large number of medical students, interns and nurses who have had unsuspected tuberculosis of the tonsils has been an interesting feature of this investigation. Von Scheibner[80] also noted the frequency of tonsil tuberculosis in nurses. This phase of the incidence of tonsil tuberculosis cannot now be presented by a statistical method,

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[42] Read at the meeting of the American Association of Pathologists and Bacteriologists, New York, 1917.

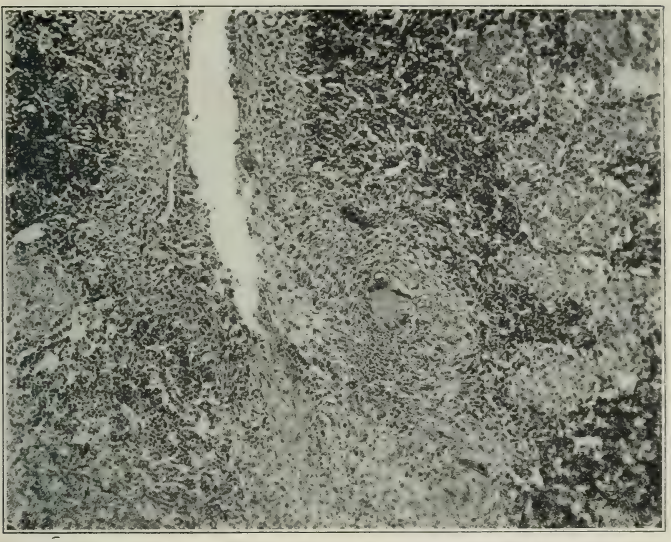

Fig. 7.—Photomicrograph of giant cell and epithelioid tubercles in and beneath the mucosa at the bottom of a crypt. Hemalum and eosin stain. Zeiss "B," without ocular.

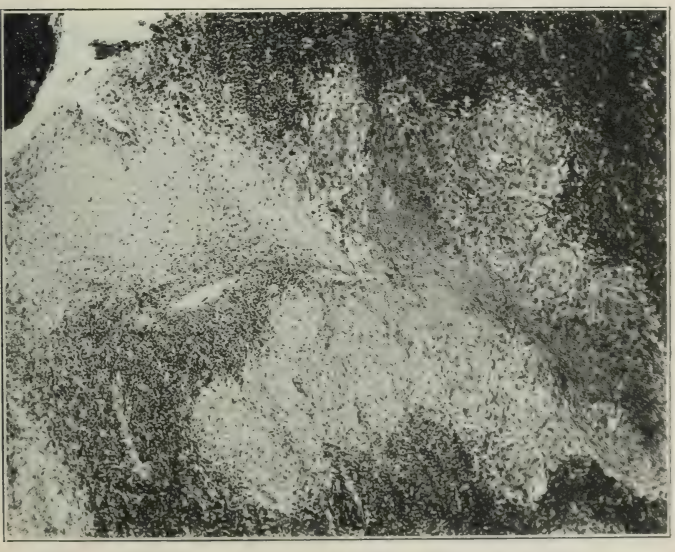

Fig. 8.—Photomicrograph showing submucous confluent epithelioid tubercles with some caseation. Toluidin blue stain. Zeiss "B," without ocular.

but the frequency in these groups has been striking, and can have no other explanation than that most of these cases represent a primary focal tuberculosis.

HISTOPATHOLOGY OF TONSILLAR TUBERCULOSIS

The histologic evidences of tuberculosis, as they are met with in the tonsil, differ in no respect from those found elsewhere in lymphadenoid tissue and require no descriptive characterization as far as their recognition is concerned (Figs. 3 and 4). The distribution of the lesions, their location in respect to crypt epithelium and follicles and the various types of tuberculous processes, are the considerations of chief interest.

The tuberculous tonsil is diagnosed clinically but rarely. Except in the very small percentage of cases showing extensive, ulcerative, lupus-like lesions these tonsils show nothing characteristic. The tuberculous tonsil may be either hyperplastic or atrophic, prominent or buried. As can be noted in the literature, the inexpert frequently interpret plugs of caseous debris, expressed from the mouths of the crypts, as gross evidence of caseation necrosis due to tuberculosis. In those cases in which clinical diagnoses of tonsil tuberculosis have been substantiated microscopically, the diagnoses have usually been based on the presence of tuberculous cervical nodes or of pulmonary lesions moderately well advanced, and not on anything manifest in the tonsils themselves.

TABLE 5.—Distribution of Lesions Among Faucial and Pharyngeal Tonsils

One Faucial Tonsil	Other Faucial Tonsil	Pharyngeal Tonsil	Number of Cases
Positive	Positive	Positive	2
Positive	Positive	Not examined	44
Positive	Positive	Negative	3
Positive	Not examined	Positive	0
Positive	Negative	Positive	1
Not examined	Not examined	Positive	1
Negative	Negative	Positive	11
Positive	Negative	Not examined	123
Positive	Negative	Negative	9
Positive	Not examined	Not examined	10
Total number of cases			204

The coincidence of tuberculosis in both faucial tonsils or in one or both faucial tonsils and pharyngeal tonsil is shown in Table 5. From this table it will be seen that of the 182 positive cases, in which both faucial tonsils could be examined, 133 showed unilateral lesions as compared to forty-nine with bilateral involvement. Of twenty-six positive cases, in which all three tonsils (two faucial and pharyngeal) were examined, the lesions were triple in two cases, double in four cases, and single in twenty cases. These twenty cases consisted of

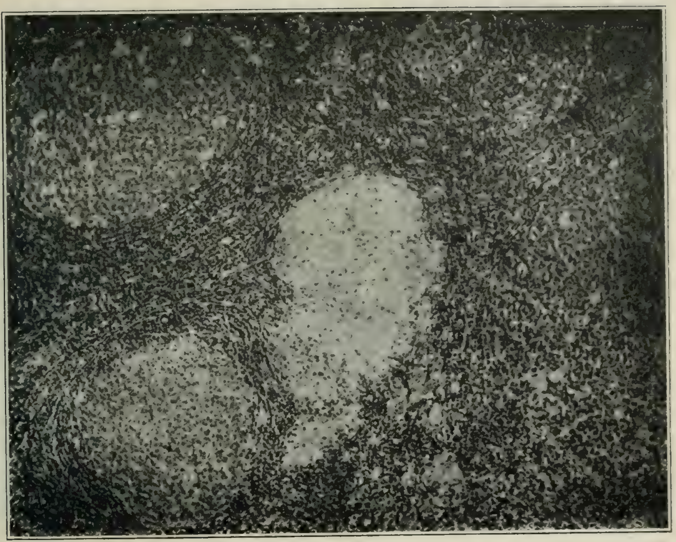

Fig. 9.—Photomicrograph of typical epithelioid tubercle from a crypt infection case. Note noninvolvement of lymph follicles. Toluidin blue stain, Zeiss "B," without ocular.

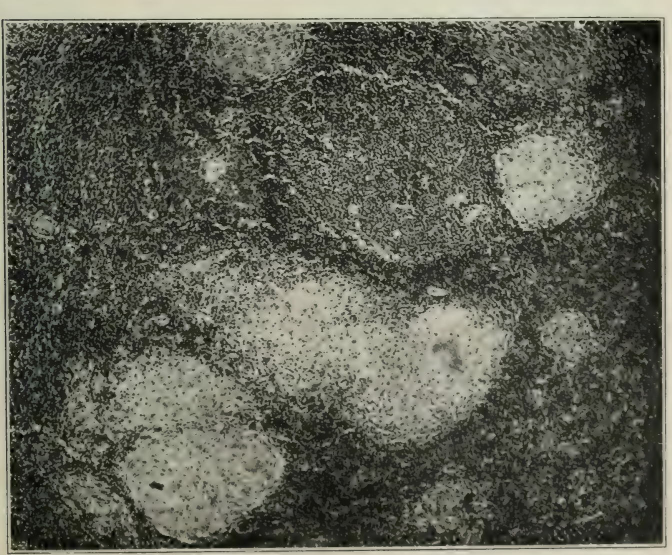

Fig. 10.—Photomicrograph of epithelioid and giant cell tubercles from a crypt infection. Lymph follicles are uninvolved in spite of extensive character of lesion. Toluidin blue stain, Zeiss "B" objective, no ocular.

eleven cases of tuberculosis of adenoids only, and nine cases of tuberculosis of one faucial tonsil only.

The extent of the tuberculous process was gaged by recording the number of tubercles as "many," "few," or "solitary." As measured by this rough scale, 120 cases showed an extensive involvement fifty-three cases few tubercles only, and thirty-one cases but a single tubercle.

The most common histologic type of tonsil tubercle is the epithelioid tubercle, with or without giant cells (Figs. 5 and 6). Not infrequently numerous very large giant cells occur. Caseation occurs proportionately less frequently than in tuberculosis of the lungs and bronchial nodes. Of the 204 positive cases, only thirty-five showed caseation worthy of note and these were chiefly cases in which the tubercles were sufficiently numerous to be confluent.

The distribution of the lesions within the tonsil is a matter of the greatest importance. Three types may be recognized, and these may occur either alone, or in combination with each other. The first, and most common, is that which may be termed the crypt infection, a manner of distribution which was clearly present in more than 60 per cent. of our cases. The actual incidence of this type is undoubtedly much higher than can be demonstrated, due to the fact that those ramifications of the crypts which occur in the third dimension cannot be appreciated, except by methods of reconstruction from serial sections. In the crypt infection, the tubercles tend to be submucous in position and are confined to the area of one or more crypts (Figs. 7, 8, 9, 10, 11, 15, 17, 18, 19, 20). These crypt areas are often surprisingly extensive. One-fourth or one-third of a tonsil may be tuberculous, and yet a careful tracing of the crypts in that area will show that they have a common mouth. The slitlike character of the crypts likewise increases the apparent extent of the area involved from a single crypt, for the lateral extensions are rarely borne in mind. The more important connective tissue septums serve to define the areas of individual or closely related crypts and groups of lesions bounded by such septa may be assumed to have a common origin. In this type of tonsillar tuberculosis the lymph follicles are involved not at all or only late in the process and the lesions are very frequently unilateral.

As by far the most common type of tonsil tuberculosis, the "crypt infection," with its localized lesions, submucous tubercles and usual failure to involve the lymph follicles, has been the form described by most authors. Piffl[illegible] noted the submucous position of the tubercles in adenoid tuberculosis. Robertson[illegible] designated three or four crypts, emptying into the supratonsillar fossa as "the infecting crypts of the tonsil." Mitchell[illegible] found that tuberculous lesions occurred in three

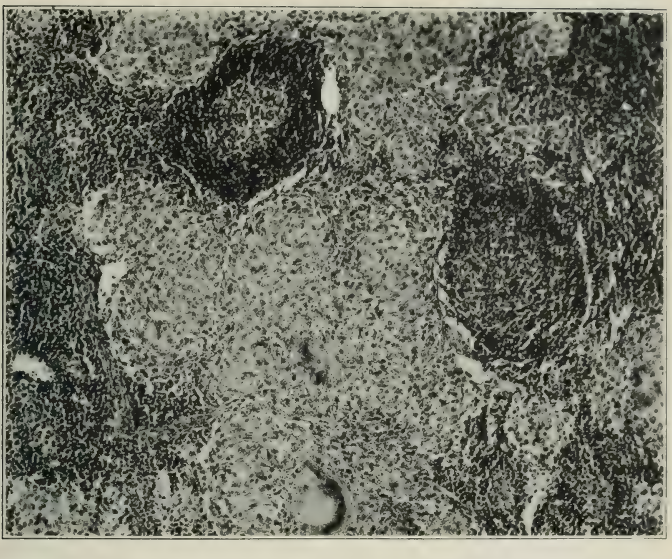

Fig. 11.—Photomicrograph showing extensive tonsillar tuberculosis. Crypt infection type. Lymph follicles remain uninvolved. Hemalum and eosin stain. Zeiss objective "B," no ocular, bellow's length, 150 cm.

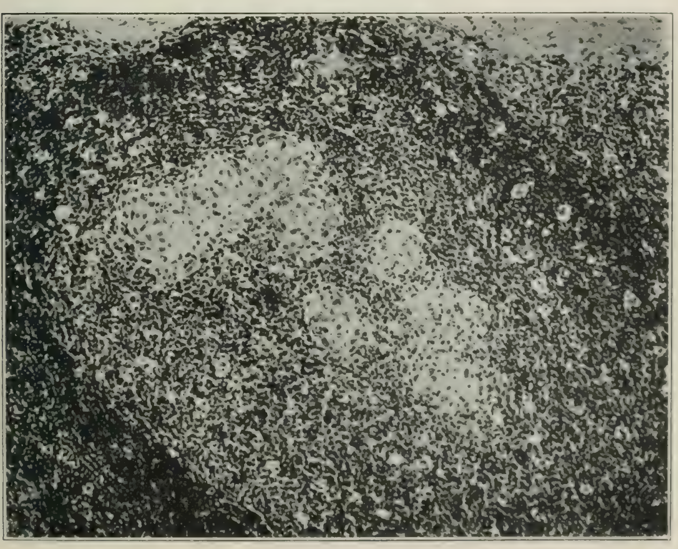

Fig. 12.—Photomicrograph showing epithelioid miliary tubercles in lymph follicle of tonsil. Diffuse miliary tonsillar tuberculosis. Toluidin blue stain. Zeiss objective "B," no ocular.

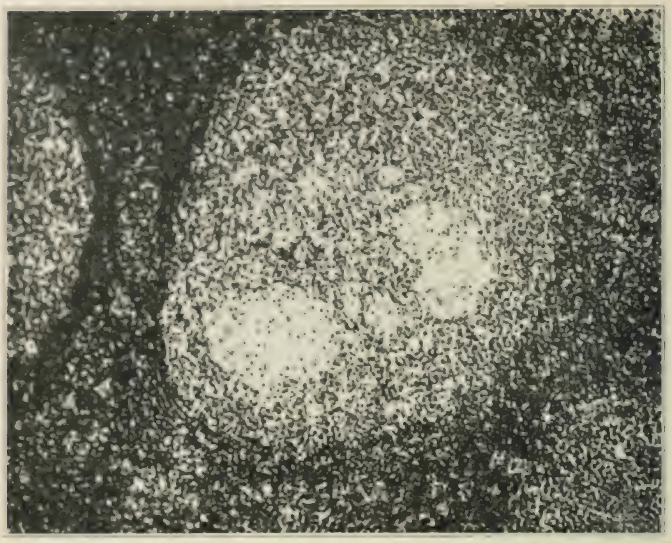

Fig. 13—Photomicrograph showing epithelioid miliary tubercles in lymph follicle of tonsil. Diffuse miliary tonsillar tuberculosis. Toluidin blue stain. Zeiss objective "B," no ocular.

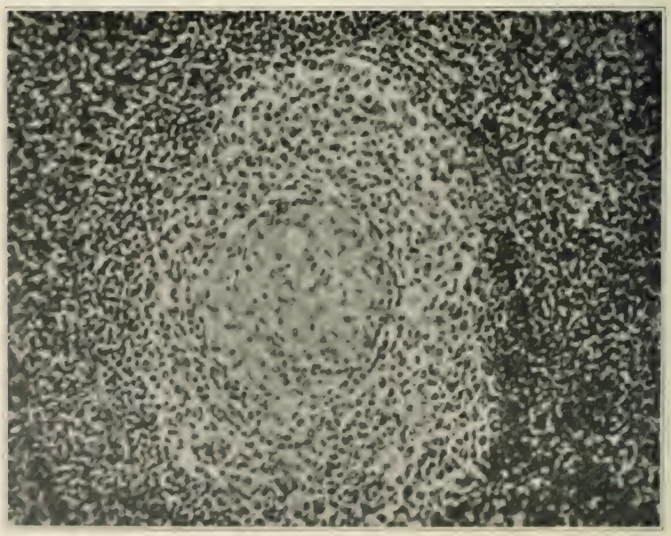

Fig. 14.—Photomicrograph showing epithelioid miliary tubercle in germ center of follicle. Note formation of tubercle about wall of arteriole of the follicle. Diffuse hematogenous miliary tuberculosis. Toluidin blue stain. Zeiss "DD," no ocular

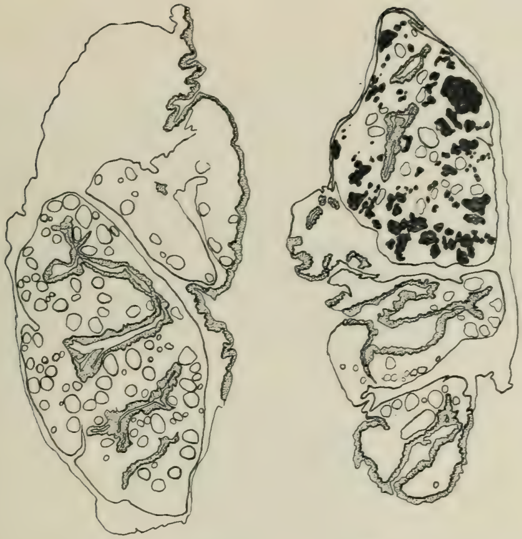

Fig. 15.—Right and left tonsils from Case 1294-U. Tracings of vertical sections made by direct projection through 48 mm. objective. Solid black indicates areas of tuberculosis; the open circles, the more prominent follicles. Tuberculosis confined to a single crypt area of one tonsil only. Crypt infection, limited by septum. Follicles not involved.

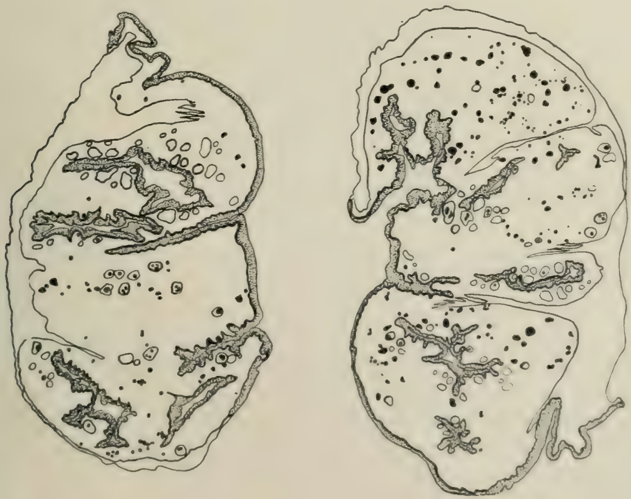

Fig. 16.—Tracings of right and left tonsils of Case 3832-U. The tubercles are shown in solid black and are found to be nearly uniformly distributed throughout both tonsils. Their location is not determined by crypts or septa and many are found in follicles. Hematogenous miliary tuberculosis.

situations: surrounding the deeper parts of the crypts, especially the supratonsillar group; immediately under the mucous membrane near the mouths of the crypts; and deep in the tonsil, close to the posterior capsule. At the bottom of the crypts, near the capsular surface, was the most common location as found by Crowe, Watkins and Rothholz.[29]

The second group of cases includes those which are recognized as tuberculous by their gross appearances—the ulcerative lupuslike lesions. These result from extensive, coalescing, multiple crypt infections such as may be found in the massive auto-infections of the tonsil in some open cases of pulmonary tuberculosis, or from involvement of the tonsil in an ulcerative tuberculosis of mouth or pharynx.

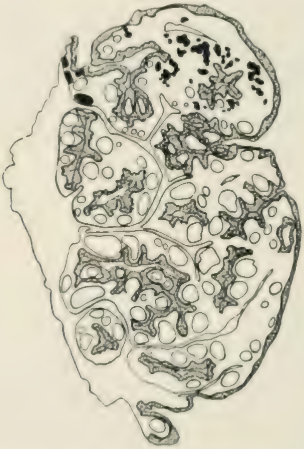

Fig. 17.—Tracing showing areas of tuberculosis (solid black), crypt systems and prominent follicles in one tonsil of Case 583-P. A crypt infection. Other tonsil not involved.

The third type of tonsil tuberculosis is one which has not, to our knowledge, been described previously, and the significance of which has not hitherto been established. In this form, the lesions are usually bilateral, are widely scattered throughout the tonsil rather than grouped in crypt areas, and characteristically involve the lymph follicles and even the germ centers of the follicles (Figs. 12, 13, 14, 16). It is, therefore, in these three particulars, in sharp contrast to the form described in the first group. The occurrence of tubercles within the germ centers gives a picture strikingly unlike the usual tonsillar tuberculosis. Cases are met with in which the tubercles, even though very numerous throughout the sections, are found in no other location.

Observations of tubercles so situated have been recorded occasionally in the literature. Pluder and Fischer [13] found in one of their cases of adenoid tuberculosis that the tubercles were situated partly within and partly between the follicles. In one of his cases, also, Ruge [43] described the tubercles as occurring singly and chiefly within the follicles. In Gottstein's [23] Case 3 almost the entire section of pharyngeal tonsil was involved and there were numerous tubercles in the follicles. In his Case 5 there were tubercles in the follicles of both adenoids and tonsils, and in Case 6 some follicles contained small tubercles with giant cells. These authors, however, do not consider these cases as belonging to a distinct group.

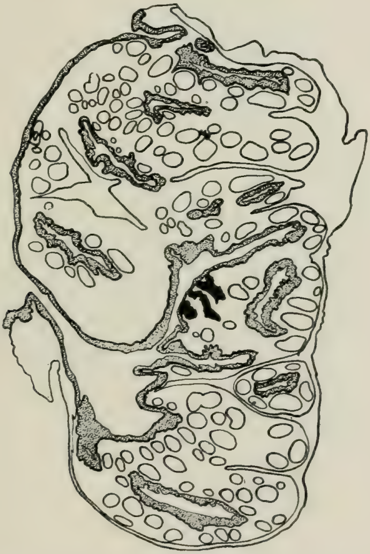

Fig. 18.—A sharply localized crypt infection in one tonsil of Case 639-O. Other tonsil free.

We have had sixteen cases of tonsil tuberculosis with the tubercles occurring chiefly or exclusively in the germ centers. Of these, nine showed bilateral lesions and of the other seven, there were three in which only a single follicle was involved, and hence the unilateral character was without significance. There were only two instances in which the pharyngeal tonsil was also examined. In one of these, all three tonsils showed a diffuse follicular distribution while the other case was one of those in which one follicle only was involved.

It is our belief that an important clinical significance attaches to the recognition of the type of tonsil tuberculosis. The "crypt area" infections, submucous, usually unilateral and involving the follicles very late, if at all, are focal processes, infections from without, either primary or autoinfections. The scattered lesions, usually bilateral and occurring chiefly in the follicles, are the result of a hematogenous dissemination of tubercle bacilli When this is borne in mind, it will be seen that many mixed cases will occur. These should be found particularly in those patients who have advanced pulmonary tuberculosis with sputum rich in organisms, and who suffer at the same time from general miliary dissemination. This is found to hold true in cases of tonsillar tuberculosis which we have studied postmortem (a class of material not included in the statistical analysis given here). Tonsils from such patients usually show one or more definite areas of crypt infection and a miliary tuberculosis of the follicles comparable in degree

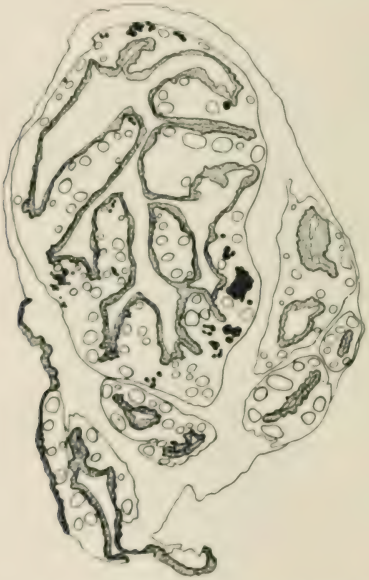

Fig. 19.—Case 1495-V. Tonsillar tuberculosis involving one tonsil only. On casual examination lesions might seem to be quite widely scattered, but the tracing shows that they are confined to a single crypt area. They do not involve the follicles.

to the miliary dissemination in other organs; such as liver, spleen and kidneys. These points will receive further consideration in the general discussion which follows.

DISCUSSION

It is not within the scope of this paper to attempt to make a case by case comparison of the histopathologic changes in the tonsil with the clinical data. There are, however, certain clinical considerations which must be given further explanation.

It has already been pointed out that from the limitations of the method employed, the incidence of tonsil tuberculosis, here shown to be 2.35 per cent., is of necessity lower than the actual incidence by an unknown amount. It must be emphasized, also, that this incidence is one of active lesions only. Hyalin scars, areas of fibrosis, more or less rounded in outline and poor in blood vessels, are frequently met with in tonsils showing no active lesions. It is probable that most of these areas are healed or healing tubercles. They cannot be differentiated from the older tubercles in tonsils showing miliary tubercles of all ages. It is our opinion that with all the healed lesions included and all por-

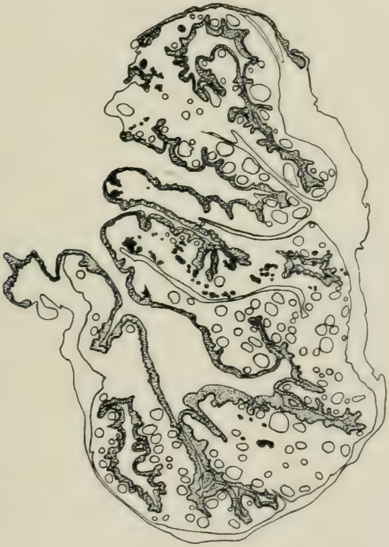

Fig. 20.—Case 1500-S. Tracing showing in solid black the distribution of tubercles in a case with apparently multiple crypt infections. Follicles (open circles) are not involved in the tuberculous process.

tions of the tonsil systematically examined, tonsillar tuberculosis would be found to be as universal as is pleural and pulmonary tuberculosis. The solitary tubercles, occurrence of which, in an active stage, was noted in thirty-one of our 204 cases, in general have no further significance than that they are a part of this universal infection, their discovery being purely accidental. In some instances they may indicate the dissemination of a limited number of bacilli with the production of but few miliary tubercles.

The preponderance of epithelioid and giant cell tubercles over caseating lesions in tonsillar tuberculosis suggests that the type of the infecting organism is not infrequently one of only moderate virulence. The histologic character of the lesions, determined by the balance between the necrosing agent and the reparative activity of the tissues, in many cases points to the bovine rather than the human type of tubercle bacillus as the infecting agent. Judgment on this point is of necessity uncertain and cannot go much beyond a general impression, but the results of bacteriological examination of tuberculous tonsils and cervical nodes prove of interest in this connection. Mitchell [22] identified the strain in twenty-six cases of tonsil tuberculosis in children and found twenty to be bovine and six human. In seventy-two consecutive cases of tuberculous cervical nodes the same author [28] found sixty-five bovine and seven human. Park and Krumwiede [43a] found the same preponderance of the bovine strain in cervical node tuberculosis in young children while in older children the human strain became the more common. Under 5 years, they found six human and twelve bovine; between 5 and 16 years, nineteen human and eight bovine; 16 years and over, nine human, no bovine. In a large series of tuberculous cervical nodes, Griffith [44] found the proportion of bovine infection to decrease regularly from 85.7 per cent. under 5 years of age to 19.0 per cent. at 20 years and over. It seems reasonable, therefore, to attribute the relative freedom from caseation to the bovine strain of organism as the more common invader, particularly in the tonsils of young children.

The crypt infection type of tonsillar tuberculosis can be explained only on the basis of the entrance of the infection from the mucosal side and not by the hematogenous or lymphogenous routes. The characteristic unilateral, or better, monotonsillar, involvement, the limited localization of the process within the affected tonsil, the frequent sub-

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43. Ruge: Die Tuberculose der Tonsillen vom klinischen Standpunkte, Arch. f. path. Anat. u. Physiol. **144**:431, 1896.

43a. Park and Krumwiede: The Relative Importance of the Bovine and Human Types of Tubercle Bacilli in the Different Forms of Human Tuberculosis, J. M. Research **23**:205, 1910.

44. Griffith, A. S.: Types of Tubercle Bacilli in Cervical and Axillary Gland Tuberculosis, Lancet **1**:216, 1917.

mucous position of the tubercles and the avoidance of the follicles all point to mucosal infection. This may, of course, be either a primary infection or a secondary, that is, autoinfection. We can be certain that both occur in our series. Those cases in which the crypt infection is not monotonsillar, but double or triple, are usually, but not necessarily, cases of autoinfection and should be examined carefully for open lesions elsewhere in the respiratory tract. A majority of the monotonsillar and some of the double and triple crypt infections are primary tonsil tuberculosis. These are the patients who show no evidence of active tuberculosis elsewhere in the body and in their subsequent history often show no evolution of the disease. It must be emphasized that the absence of clinical evidence of active tuberculosis elsewhere in the body would have little value if we had not previously established the fact that the type of infection of which we are now speaking comes through the mucosa. It requires an open lesion for the crypt type of auto-infection and clinical evidence should be forthcoming either before or after the occurrence of tonsillar invasion. The monotonsillar crypt infection has been very common in nurses, interns and upper class medical students. Many of these cases have been followed up and have shown no further lesions. We are convinced that most of these cases are examples of primary focal tonsil tuberculosis. The infectious material is either inspired or ingested. Experimental evidence of the possibility of tonsillar infection in this manner is abundant. Feeding experiments with infected material, such as were carried out by Orth,[4] Baumgarten[45] and others, and the infusion of lamp black into the pharynx by Hendelsohn[46] and injection of carmin into the tonsillar crypts by Goodale[47] have all shown that both living organisms and inert particles present in the pharynx and tonsillar crypts pass into the tonsil with ease.

On the other hand, the third type of tonsil tuberculosis, the diffuse follicular miliary tuberculosis, in all of its characteristics points to a hematogenous origin, the terminals of the follicular arterioles being the seat of lodgment of the bacilli. If this process were frequently unilateral, a retrograde lymphogenous metastasis from the cervical nodes might be considered, especially in view of the work of Blum[48] who reported that both inert substances and living organisms injected into the cervical nodes of guinea-pigs were subsequently found in the tonsils and in the oral cavity. Such a retrograde metastasis in the slowly moving lymph stream, subjected to the irregular pressures produced by the contraction of nearby muscles, is to be expected. But the type of tonsil tuberculosis in which the tubercles occur chiefly in the follicles is usually bilateral and frequently universal in its involvement of the tonsils. The work of Goodale [47] and of Hendelsohn [46] has an application here not anticipated by those investigators. The former found that carmin particles injected into the tonsillar crypts penetrated all other portions of the tonsil more promptly than the follicles. In tonsils removed up to two hours after injection none was found in the interior of the follicles. Even at five and ten days, although the interfollicular lymph spaces contain much carmin the interior of the follicles showed none and there was but little in the neighborhood of the germ centers. Hendelsohn [46] found that only with more intense applications of dust to the tonsil were any particles found within the follicles and he notes the analogy between his observation and that of Arnold [49] who found that the follicles and germ centers of lymph nodes remain relatively free even when the interfollicular tissue is loaded with dust.

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[45] Baumgarten: Ueber die Uebertragbarkeit der Tuberculose durch die Nahrung, Centralbl. f. klin. Med. **5**:25, 1884.

[46] Hendelsohn: Ueber das Verhalten des Mandelgewebes gegen aufgeblasene pulverförmige Substanzen, Arch. f. Laryngol. u. Rhinol. **8**:476, 1898.

[47] Goodale: Absorption von Fremdkorpern durch die Gaumentonsillen. Arch. f. Laryngol. **7**:90, 1898.

[48] Blum, S.: Tonsils Excretory Organs for Cervical Glands: Preliminary Report, Arch. Pediat. **32**:837, 1915.

It is not within the scope of this paper to enter at length into a discussion of the relationship of tonsillar to cervical gland and pulmonary tuberculosis. Our cases include many in which cervical nodes were examined histologically after the tonsils were found to be tuberculous. In some of these the nodes were also found to be tuberculous. In other cases, extensive tonsillar tuberculosis was unaccompanied by cervical gland lesions. The converse was even more frequently noted, the tonsils from patients with extensive cervical node lesions failing to show any lesions. Nevertheless, the tonsil must be considered the most important portal of entrance in cervical gland tuberculosis.

The relationship to pleural and pulmonary tuberculosis is even more difficult to analyze. The work of Grober [24] in tracing carbon particles injected into the tonsils to the pleura and pleural space by way of the cervical lymphatics is much quoted. Van Zwaluwenburg and Grabfield [50] find that patients with tonsillar tuberculosis almost invariably show, in stereograms of the thorax, changes in the apical pleura which they believe are due to tuberculosis. However, we have failed to find tuberculosis in the tonsils removed from a number of such cases.

From the pathologist's standpoint, an incidence of active tonsillar tuberculosis of more than 2.35 per cent. should not, in itself, be considered an argument for tonsillectomy. The facts here presented, however, do lead to the belief that it is advisable to remove the tonsils in cases of known cervical nodes or pulmonary tuberculosis in the hope of removing an active focus of dissemination.

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[49] Arnold: Untersuchungen über Staubinhalation und Staubmetastase, Leipzig, 1885.

[50] Van Zwaluwenburg and Grabfield: Papers now in press, to appear in American Review of Tuberculosis, 1921, and to which I am permitted to refer through the kindness of the senior author.

CONCLUSIONS

1. The systematic search of a limited number of microscopic sections, so oriented as to show in each the entire surface of a vertically bisected tonsil, is the only practicable routine method for detecting tonsil tuberculosis.
2. The incidence of active tonsil tuberculosis in a series of 8,697 consecutive cases was found to be 2.35 per cent. This minimum figure would have been increased by an unknown, but probably small, amount if it had been possible to examine all portions of each tonsil.
3. The incidence in respect to sex shows tonsil tuberculosis to be slightly more common in females than in males at practically all ages.
4. In the series of 204 positive cases here reported, the range of ages was from 2 to 59 years. The incidence in various age groups depends largely on the character of the population from which the material is derived, the incidence being particularly high in institutions for the care of children and among medical students, interns and nurses.
5. Tonsil tuberculosis may be divided into three types: focal crypt infections; ulcerative lupus-like lesions; and diffuse miliary tuberculosis.
6. The crypt infection is the most common type, is usually unilateral, involves one or more crypt areas only and avoids the lymph follicles. Some of these cases are autoinfections in open respiratory tract tuberculosis but the majority must be considered cases of primary focal tonsil tuberculosis.
7. The ulcerative lupus-like lesions result from the coalescence of crypt infections at the mouths of crypts or from direct extension from neighboring surfaces.
8. The diffuse miliary tuberculosis is usually a bilateral or, if the pharyngeal tonsil is examined, a universal tonsil lesion. The tubercles are widely scattered and occur almost exclusively in the follicles and germ centers. This type can best be explained as a hematogenous miliary dissemination.
9. Mixed types occur, as in patients with open pulmonary tuberculosis, in which autoinfection may be associated with hematogenous miliary tuberculosis giving a combination of crypt infections with diffuse miliary tubercles.[51]

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[51] The following references will also be found to have bearing on the subject of tonsil tuberculosis:

Abraham, P. S., and Franks: Tubercle of the Tonsils, Dublin J. M. Sc. **80**:346, 1885.

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Koplik, H.: Tuberculosis of the Tonsils and the Tonsils as a Portal of Tubercular Infection, Am. J. M. Sc. **126**:816, 1903.

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The original pathologic diagnoses of the greater part of the material on which this study is based were made by Dr. A. S. Warthin. To him I acknowledge my indebtedness for the use of this material, as well as for many helpful suggestions throughout the prosecution of the work.

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83 (1458)

The pathology of dichlorethylsulphide (" mustard gas ") poisoning.

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The specific microscopic pathology of the local lesions of dichlorethylsulphide poisoning consists in degeneration and necrosis of the cells with which it comes in contact. The earliest microscopic change is pyknosis of the nucleus and cell body, followed by hydropic degeneration, liquefaction or coagulation necrosis. In the skin, hyperemia, with regeneration of the damaged cells, pigmentation, vesicle formation, desquamation of the dead epidermis or eschar formation mark varying stages of severity of the lesion. The degenerative changes extend deepest in the hair follicles and sweat glands. In mild burns without vesication the papillary layer of the corium may show a greater degree of necrosis than the epidermis itself, thus explaining the frequent occurrence of Nikolsky's sign. Large pigmented chromatophores may be the only living cells left in the papillary layer. In severe burns the necrosis may extend entirely through the corium. In the cornea, pyknosis and simple or coagulation necrosis of the corneal epithelium and interstitial substance, even to the endothelial layer, in extent varying with the degree of exposure, constitute the microscopic features. On the conjunctivæ the epithelium shows pyknosis, hydropic degeneration, liquefaction necrosis, or there may be a deeper necrosis extending into the subconjunctival tissues. The conjunctival surface suffers to a less degree proportionately than the epidermis. On the mucous membranes the epithelium shows pyknosis, hydropic or mucoid degeneration, desquamation, liquefaction or coagulation necrosis. The necrosis may extend into the submucosa, but the depth of the lesions on the conjunctivæ and the mucous membranes of the respiratory tract is never so great from identical exposures, as it is in the skin. Following the necrosis there is marked hyperemia, and the development of an edema, more marked in the subcutaneous and subconjunctival tissues in animals, but less marked in man. Human skin, however, shows a much greater tendency to vesication. The blood vessels in the necrotic area are killed, the blood cells hemolyzed to some extent without thrombus formation or much extravasation, except minute hemorrhages by diapedesis. Following the lesion there is a demarcating inflammation, with slow regeneration, repair or cicatrization. The regeneration of the epidermis proceeds from the epithelium of the sweat and sebaceous glands. On the mucous membranes there results in the severe cases a localized eschar or ulcer, or a more diffuse diphtheritis. With secondary infection the inflammatory process becomes purulent or suppurative. The influence of secondary trauma and infection is well shown in the early development of deep areas of decubitus in the injured regions of the skin. Multiple furuncles may develop, or large cutaneous areas become gangrenous. In the eye purulent involvement of the anterior chamber, iris and ciliary body may occur, or even a suppurative panophthalmitis. In the respiratory tract secondary infection of the injured mucosa may lead to a purulent bronchopneumonia.

The internal organs in animals with mustard gas lesions of the skin, eyes, respiratory or gastrointestinal tract offer nothing of a specific pathologic nature. There is general congestion, marked splanchnic congestion, acute catarrh of the intestines and, in infected cases, some cloudy swelling of the kidneys.

In fatal cases the cause of death is to be found in shock, secondary infection with toxemia, or local conditions as laryngitis, tracheitis, bronchitis and bronchopneumonia. It is also possible that the entrance into the body of shell fragments carrying liquid dichlorethylsulphide might cause a relatively speedy death through absorption.

At the site of subcutaneous injections there is found a local eschar with demarcating hemorrhage, edema and inflammatory infiltration; in the large veins into which injections have been made, no changes have been found except occasional thrombosis.

The general pathology of the injected cases presents a specific pathologic picture in the intestinal tract in the form of a severe mucoid, desquamative or necrotic enteritis, the intestinal epithelium showing the most marked hydropic or mucoid degeneration, even to liquefaction necrosis. Similar changes may be found in the epithelium of the bile ducts. In a certain number of cases the spleen, lymph nodes and hemal nodes show a marked hemosiderosis, the hemosiderin being contained in large hemophages. It is most probable that these evidences of increased hemolysis are explainable by the extravasations and blood destruction occurring at the site of the injection. No specific changes were observed in the blood-forming organs. In the other organs no pathologic changes but congestion have been found, with the rare exception of emboli or thrombi.

Mode of Action.—The cause of death in intravenous and subcutaneous injections would appear to be the direct action of minute quantities of free dichlorethylsulphide or some poisonous product resulting from its decomposition, upon the cells of the central nervous system. It has been assumed that the pathologic action of dichlorethylsulphide is due to its hydrolysis within the tissue cells. The products of this hydrolysis, hydrochloric acid and dihydroxyethylsulphide, when injected into the blood, do not produce the same effects. Dihydroxyethylsulphide and hydrochloric acid, when injected into the circulation in much larger doses than would result from the hydrolysis of the fatal doses of mustard gas, are harmless. The effect upon the cells of the central nervous system may, however, depend upon hydrolysis, with the liberation of hydrochloric acid (*Marshall*), in these cells of minute quantities of mustard gas in the circulation, or these cells may be injured without such hydrolysis occurring. It is probable that the gastrointestinal catarrh resulting from the injections of dichlorethylsulphide is secondary to the nervous injury, rather than to an excretion of the poison or poisonous products through this tract, although this point remains unsettled. No positive tests for dichlorethylsulphide or dihydroxyethylsulphide have been obtained in the bile, intestinal contents, or urine. Incidentally, it has been shown that the platinic chloride-sodium iodide color test for dichlorethylsulphide is not applicable to the body fluids or extracts of various organs and tissues, as similar color changes are produced by some of these.

Treatment.—The principles of treatment to be applied to mustard gas injuries are primarily those that will remove any of the gas remaining, lessen necrosis, prevent infection and promote healing. Our experience leads us to recommend the use of Dakin's solution in irrigation or full baths for the skin lesions, and a 0.5 per cent. solution of dichloramine-T for the eye lesions, and also as a mouth wash. The fluid intake should be forced when the urine is concentrated. Pressure must be removed from all injured areas. Air-excluding and infection-including protections, such as oily dressings, paraffin sprays and coatings, zinc stearate, olive oil, vaseline, etc., should not be used, unless there is an active and persistent germicidal agent present as in the case of sodium stearate impregnated with chloramine-T, or the chlorcosane solution of dichloramine-T.

Sequelæ.—Among the most important sequelæ of mustard gassing is the apparent increased susceptibility to influenza, bronchitis, pneumonia and tuberculosis following lesions of the respiratory tract cicatricial contractions, pulmonary fibrosis. The respiratory infections may become chronic and death from these may take place months after the gassing. Persistent aphonia, due to local lesions or as one expression of a traumatic neurosis, is not a rare sequel. Chronic disturbances of vision are also in part the result of local changes and in part psychical. In the skin conditions of chronic eczema, itching and desquamative dermatitis, and pigmentation occur as sequelæ. Leucotrichia has also been observed. It is safe to predict that a development of squamous cell carcinoma in the extensive cicatrices, following mustard gas lesions will take place fifteen to twenty-five years later as in the case of extensive thermal burns. Finally, the psychical disturbances following mustard gassing should not be minimized.

As to its use in warfare, mustard gas is a disabling rather than a killing agent. Under the actual conditions of the field the great majority of mustard gas casualties are likely to be of a nature tending to incapacitate the injured for service for a number of days or weeks, or even for months. Added to this, the insidious character of this invisible fire, painless and often unrecognized in its action, makes mustard gas a potent factor in undermining the morale of the troops exposed to it.

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82 (1457)

The toxic action of dichlorethylsulphide (" mustard gas ").

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The investigations recorded in these two papers are founded upon numerous series of animal experimentations and also clinical observations of human mustard gassing.

1. *Local Action: Skin.*—Dichlorethylsulphide ("mustard gas"), in liquid or in vapor form, even in very low concentrations, is an escharotic poison for the animal tissues (skin, conjunctivæ, cornea, mucous membranes of respiratory and gastrointestinal tracts) with which it comes in direct contact. The degree of the injury is proportionate to the concentration of the gas, the time of exposure, individual susceptibility, and local physical conditions, such as moisture, sweating, warmth, pressure and friction. The escharotic action is, for the greater part, painless, the anesthetic effect being especially notable upon the skin; while upon the mucous membranes its action may be more irritant, probably chiefly reflex in character. The cutaneous surfaces most susceptible are those with thinner, more delicate skin, well supplied with sweat glands and hair follicles, where sweat may collect, and which are exposed to friction or pressure, such as the axillæ, flexor surfaces, genitals, inner surface of arms and corresponding surface of trunk, inner surfaces of thighs, between the fingers, etc. There is a penetration of the gas into the sweat and sebaceous glands, and a re-solution of mustard gas vapor into the sweat or sebum occurs. The injuries are particularly striking in their insidious, slowly progressive development, becoming first apparent only some hours after the exposure. Upon human skin the lesion appears as a hyperemia, followed by vesication, eschar formation,

sloughing and slow healing, with more or less pigmentation. Depilation may occur; in severe cases the eschar may extend entirely through the corium into the subcutaneous tissues. Secondary infection and gangrene of the eschars occur invariably in cases not properly treated. Milder lesions may show only the earlier stages of hyperemia, vesication or pigmentation. In general the injuries may be classed as burns of first, second or third degree. Following extensive hyperemias in human skin a most marked pigmentation, exceeding in degree the most marked forms of solar tan may be quickly developed and fade slowly. This pigmentation may be diffuse or spotted. In human skin vesication is pronounced; in animals the cutaneous lesions are characterized by the development of marked subcutaneous edema in the injured area. The fluid of the vesicle or of the edema is nonirritating when applied to uninjured areas. In the case of human skin frequently exposed to very dilute concentrations (only perceptible by odor), an eczematous itching condition between the fingers, on the genitals, etc., may develop; rubbing or scratching of the itching part may lead to the quick development of a blister or superficial eschar (*Nikolsky's sign*). Such interdigital lesions in laboratory workers may resemble clinically those produced by the itch mite. Cutaneous areas injured by mustard gas are rendered more susceptible to trauma or other forms of injury, including new exposures to mustard gas. This local susceptibility is, however, a general one, and not a specific lowered resistance to the action of dichlorethylsulphide. Subcutaneous injections of pure dichlorethylsulphide produce painless eschars, followed by dry sloughing, with edema less marked than in the case of external cutaneous application; a hypostatic edema may develop on the animal's belly when injected in the back. In the tissues at the site of the injection and in the hypostatic edema mustard gas may be present for some days after the injection, as shown by odor and physiological reaction. The resolution of mild skin injuries is often attended by troublesome itching. Healing of the deep cutaneous eschars is very slow; during the healing of extensive deep lesions the patients complain of a sensation of tightness or contraction of the skin; large scars may be produced resembling those resulting from deep thermal burns.

The hair may be lost; but when regenerated they may be white in color.

Eye.—Upon the cornea mustard gas exerts an especially injurious action, particularly at the vertex. Within ten to fifteen minutes after exposure to dilute concentrations, degeneration or necrosis of the corneal surface may be demonstrated by the application of a 2 per cent. alkaline aqueous solution of fluorescein, the injured cells retaining a greenish fluorescent coloration. In more severe injuries the cornea may be killed throughout its entire thickness at the vertex. The mildest cases show a slight cloudiness; the severe cases present a characteristic porcelain appearance of bluish white opalescent cloudiness, often with a more opaque band or line running horizontally across the cornea just below its transverse diameter. The injury to the conjunctiva is shown by the development of a more or less severe catarrhal, seropurulent or purulent conjunctivitis with marked edema of the subconjunctival tissues leading often to "ruffling" of the lids, entropion, ectropion or a combination of these. Even the lighter cases tend to run a chronic course with disturbances and reduction of vision. In the severe cases cicatrization and vascularization of the cornea take place slowly with resulting impairment or loss of vision. The injured eye is more susceptible to infection; and in infected cases suppurative panophthalmitis may develop with complete destruction of the eyeball. Recovered cases of mild mustard gas conjunctivitis often show an increased sensitivity to the action of light, dust, and other irritants, including mustard gas fumes.

Respiratory Tract.—Upon the mucosa of the respiratory tract mustard gas vapor produces a local injury to the epithelium as shown by the development of a catarrhal, desquamative, membranous, diphtheritic or purulent inflammation (rhinitis, stomatitis, pharyngitis, laryngitis, tracheitis and bronchitis), these lesions being most severe in the nose, back of tongue, palate, pharynx and larynx, decreasing in intensity downwards. Coryza, salivation, dryness of mouth and throat, aphonia and persistent cough are the chief symptoms, with physical signs of laryngeal, tracheal and bronchial involvement, and atelectasis, emphysema and edema of the lungs. As a result of secondary infection a purulent bronchopneumonia may develop.

Gastrointestinal Tract.—Through the swallowing of air, saliva or secretions from the upper respiratory tract containing mustard gas, or from the ingestion of contaminated food local corrosive action upon the alimentary mucosa may be produced, varying from a catarrhal inflammation to large areas of eschar formation with resulting gastric ulcer, perforation, etc. The symptomatology of the mildest lesions is covered up by that resulting from the more severe burns elsewhere; the more severe ones will produce marked symptoms referable to the stomach and intestines.

2. *General Action: Susceptibility.*—There exists a racial (whites more susceptible than negroes) and an individual susceptibility to the action of dichlorethylsulphide, particularly in the case of the skin and probably also of the respiratory tract. The individual susceptibility, in some cases at least, is associated with the characteristic stigmata and symptomatology of the thymicolymphatic constitution. Acquired susceptibility is not specific. Animals show also generic and individual differences in sensitivity to mustard gas.

Systemic Action.—There is no evidence of any systemic poisoning by the absorption of dichlorethylsulphide from the skin, eyes or mucous membranes of the respiratory or gastrointestinal tracts. There is no metastatic action of the gas from the site of local external application.

Shock.—In all severe cases of mustard gas burns of skin, eyes, or mucous membranes there is usually the clinical picture of severe shock, in the form of intense pallor, depression of pulse and temperature, general collapse, nausea and vomiting. The mildest cases show no systemic reaction.

Blood and Urine.—No changes are observable in the blood or urine of mild cases. In cases with large infected burns of skin or respiratory tract, the blood presents a mild secondary anemia with leucocytosis; we have never observed leucopenia; the blood urea is increased; the urine is diminished, concentrated, and contains casts and albumin. Under forced fluids the urinary symptoms improve, and the blood urea diminishes. In severe infected cases the general picture may be that of a severe toxemia.

Intravenous and Subcutaneous Injection.—When injected intravenously or subcutaneously dichlorethylsulphide is an active poison, causing death in one to four hours intravenously and two hours to three weeks after subcutaneous injections (for rabbits intravenous injections of .0075 c.c. per kilo may be lethal within four hours), according to size of dose, individual animal, etc. When death takes place quickly, the symptoms are chiefly those of an action upon the central nervous system, such as hyper-excitability, rapid respirations, general convulsions, opisthotonos, gradual failure of respiration and circulation, coma and death. When the animal lives longer after small intravenous injections, or after subcutaneous injection, there develops a characteristic symptomatology of salivation, marked diarrhea, and fall of temperature, with marked anorexia, emaciation and depression. With subcutaneous injection of .015 to .06 c.c., death usually takes place from the fourth to the tenth day.

RUDOLF VIRCHOW—PATHOLOGIST

By Dr. CARL VERNON WELLER
UNIVERSITY OF MICHIGAN

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RUDOLF VIRCHOW—PATHOLOGIST[1]

By Dr. CARL VERNON WELLER
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IN his delightful autobiography, the elder Gross[2] writes of his first European visit in 1868.

> There were three professional men in Berlin whom, as their names had long been familiar to me as household words, I was most anxious to see—Virchow, Langenbeck and Graefe. Accordingly, early in the morning of the second day after our arrival, I went to the Allgemeines Krankenhaus in search of Virchow, the illustrious pathologist and accomplished statesman, a professor in the university of Berlin, and a member of the German parliament. The great man, upon my entrance, was in the midst of his pupils, engaged in a post-mortem examination. As my presence attracted some attention, ... I deemed it my duty, although the moment was not the most opportune, to pass my card to the professor, at the same time apologizing for the intrusion. He at once saluted me with a gracious bow, and, shaking me cordially by the hand, introduced me to his pupils and expressed his gratification at seeing me. After a few minutes spent in conversation, he resumed his knife and completed his examination. He showed me his laboratory, his lecture-room, and many of his more interesting pathological specimens, most of them prepared by his own hands. His collections of diseased hearts of children, the result of inherited syphilis, is the largest in the world, and, as he explained specimen after specimen, he became not only enthusiastic but eloquent . . . . The laboratory, or work-shop as it may be termed, of Professor Virchow is a model in its way, admirably adapted to the wants of the student for improvement in the use of the microscope and the examination of morbid specimens. . . . Microscopes are provided in great numbers, and, in fact, every facility is afforded for the acquisition of knowledge. . . . . Such a room with the necessary appliances ought to exist in every well-organized medical institution in the United States.

Dr. Gross died in 1884, so that he lived to see but the slightest realization of this wish, which has now reached a degree of fulfilment beyond the greatest anticipation either of Virchow himself or of his contemporaries.

To continue Dr. Gross's personal narrative—and I can do no better in order to give an intimate acquaintance with him whose centennial we celebrate:

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[1] A paper read at a meeting of the Research Club, University of Michigan, April 20, 1921, in commemoration of the centennials of Hermann von Helmholtz and Rudolph Virchow.

[2] Autobiography of Samuel D. Gross. G. Barrie, Philadelphia, 1887. Vol. 1, p. 231-235.

> Virchow is a most patient and laborious investigator and yet he never seems to be in a hurry. His dissections [autopsies][3] seldom occupy fewer than two and a half or three hours each. Every organ of the body is thoroughly explored. For years past his habit has been to open, every Monday morning, a cadaver in the presence of his private pupils with a view of instructing them in the art of conducting autopsies—holding the knife, using the saw, and taking notes, the whole being supplemented by microscopic inspections of the more important diseased structures. In these dissections he is, if possible, more patient even than Rokitansky, his great Viennese prototype.
>
> Virchow is a thin, slender man, about the medium height, with a fine forehead, although the head is not large, and handsome black eyes, concealed by a pair of glasses. He is deliberate in his movements, a good talker, very affable, courteous and warm-hearted—in a word, a gentleman of the higher type.

The evening before Dr. Gross left Berlin he had further occasion to appreciate Virchow's splendid courtesy. While he was the guest of honor at Virchow's own table, together with von Langenbeck, von Graefe, the oculist, Donders, Gurlt and others, the host drew from under the table a large book, which proved to be the second edition of Gross's "Elements of Pathological Anatomy," and, rising, took his guest by the hand and in a graceful speech referred to the text as one from the study of which he had derived much useful instruction and one which he always consulted with much profit.

American medicine has too seldom received that full appreciation in Berlin and Vienna that Virchow was always willing to give. In reviews and abstracted articles edited by him one is struck by the large number of English and American references included.

Nearly twenty years after the visit of Gross to Berlin, we find Sir William Osler a pilgrim in Virchow's laboratory. Perhaps it has been the growing breadth of vision during those years, but not unlikely it is the wonderful catholicity of interests, possessed by the great visitor himself which changes the character of the pen picture. Part of his narrative I must reproduce even though it reaches beyond the limits of my subject. Osler[4] writes:

> In 1884, on returning to Berlin for the first time since my student days, I took with me four choice examples of skulls of British Columbian Indians, knowing well how acceptable they would be. In his room at the Pathological Institute, surrounded by crania and skeletons, and directing his celebrated *diener*, who was mending Trojan pottery, I found the professor noting the peculiarities of a set of bones which he had just received from Madeira. Not the warm thanks, nor the cheerful, friendly greeting which he always had for an old student, pleased me half so much as the prompt and decisive identification of the skull which I had brought, and his rapid sketch of the cranial characters of the North American Indian. The profound expert, not

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[3] Bracketed words are inserted by the author.

[4] Osler, William. Virchow, the man and the student, Johns Hopkins University Circulars, 1891, XI, 17-20.

> the dilettante student has characterized all of his work in this line . . . As an illustration of his capacity for varied work, I recall one day in 1884, in which he gave the morning demonstration and lecture at the Pathological Institute, addressed the Town Council at great length on the extension of the canalization scheme, and made a budget speech in the House, both of which were reported at great length in papers of the next day.

Rudolf Virchow graduated in medicine from the Friedrich-Wilhelm Institute in 1843 with the dissertation *De rheumate praesertim corneae*. In the autumn of 1844, he became an assistant in pathological anatomy under Froriep, and in 1846 he was appointed prosector in the same clinic. He became a lecturer in the University of Berlin in 1847. Possessing vigorous political views, which would be considered liberal even today, he lost his university connections during the stormy period of 1848 and 1849, largely through the publication with Leubuscher of a half-medical, half-political journal, which they styled *Medicinische Reform*. From 1849 to 1856 he occupied the chair of pathological anatomy at Würzburg, where, working with the greatest industry, he raised his department to foremost rank and pursued investigations upon which much of his later work was based. At the end of that period, he was recalled to Berlin as professor of pathological anatomy and director of the newly established pathological institute in Berlin University, with which he was connected until his death.

To understand Virchow's relation to pathology and to medicine is to understand something of the stages through which scientific medicine has passed in the last one hundred and fifty years. We are now, and have been for some fifty years, in a period characterized by search for the etiological factor in disease. In part, the bacteriologist has been in the ascendency and we already have sufficient perspective to see the greatness of Pasteur and Koch. Among our contemporaries there may be those equally to be honored by another generation. Moreover, there are those who would have us believe that we are even now passing from the epoch of bacteriology into a period dominated by biochemistery, serology and immunology, but upon this transition, if, indeed, it should be dignified as such, light is still to be shed.

At any rate, these present-day tendencies will serve to illustrate the shifting emphasis in medical progress. Does it mean that the stage has been set for a certain scene, or that a brilliant and indefatigable worker, inspiring a group of collaborators, strides off into the unknown? As we read current medical history, the advance appears to be gradual and simultaneous along interdigitating lines. In retrospect, the advance assumes the topography of a series of steps rising from plateau-like surfaces. The highest step of the nineteenth century was the rise of microscopical pathology as established and developed by Rudolf Virchow.

Cellular pathology rose from a foundation of gross pathology. In the later half of the preceding century John Hunter had developed his wonderful museum of gross preparations of both normal and pathological anatomy. He had had the hardihood to apply objective experimental methods to the investigation of pathological problems. Through the experimental production of arterial anastomoses, he found that it was possible to ligate arteries whose flow had previously been considered essential to the life of a part. For Hunter, Virchow had the greatest admiration, and it has been said that for a long time Hunter's picture alone was found upon the walls of his laboratory. Fifty years or so after Hunter, Rokitansky in Vienna brought the period of gross pathology to its greatest height. The first autopsy protocol written in his own hand is dated October 23, 1827. In March, 1866, he achieved his thirty thousandth post-mortem examination. It is said that before his death he had access to 100,000 protocols of autopsies done by himself and his assistants. With this enormous material he brought descriptive gross pathology to a degree of perfection never before realized.

As will be noted by the dates just given, Rokitansky was well established in his field of gross pathology when Virchow read his inaugural dissertation. In fact, Virchow was still in his assistantship when the first volume of Rokitansky's *Lehrbuch der pathologischen Anatomie* appeared in 1845. With the microscope at his disposal, his independence of thought, his originality in attack, and, above all, his ability to exalt pure objective description as an end in itself made it possible for Rudolf Virchow to do for the pathology of the cell what Rokitansky had done for the pathology of the organ and tissue.

All medicine before Virchow had been burdened with mysticism, dogma and hypothesis. Witness the pertinacity with which the humoral theory survived in its varying forms, even to the extent of obscuring the earlier part of Rokitansky's work. All this Virchow was able to cast aside and, avoiding dogma, he developed a method rather than a theory.

To those who would lessen the importance of Virchow's work by reference to Bichat, it need but be said that while the latter did resolve the various organs and tissues of the body into twenty-one simple, and, as he supposed, elemental types, this analysis was done on the basis of naked-eye observation alone. Bichat did not use the microscope. Like Virchow, however, he placed the objective detailing of facts before speculation. To Schleiden and Schwann, Virchow gave full credit for the earlier development of the idea of the animal cell as interpreted in terms of cellular botany. Yet, it must be remembered that to a great extent Virchow was called upon to formulate for himself standards of normal histology as well as to describe the changes produced in the cell by disease.

No adequate analysis of Virchow's published work can be given here. Its volume is remarkable. In 1901, Schwalbe[5] and others whose assistance he invited, compiled a Virchow bibliography as their part in the celebration of the eightieth birthday of their old master. In the preface, Schwalbe himself says that a Virchow bibliography lays bare not alone the life-work of a man, but exposes as well a history of medicine and anthropology for the preceding sixty years. Requiring 118 pages, with an average of about eighteen items to the page, this list of approximately 2,000 titles bears witness to the industry, breadth of interest and critical scientific discrimination of the cellular pathologist. From all of this material I can refer only to the two most important books, to the journals developed under his leadership and to a few of the most important articles.

"Die Cellularpathologie" appeared in 1858. This book, presented in the form of twenty lectures illustrated by numerous wood cuts, placed before the world for the first time a summation of the author's views. Here was demonstrated that the principle of *omnis cellula e cellula*, which he was first to put into words, applied equally to pathological formations and to normal embryologic development. Translated into French by Picard and into English by Frank Chance, "Cellular Pathology" was seized upon with an avidity which must have surprised even its author. From that year modern pathology is to be dated. We cannot appreciate the effect upon Medicine of this new point of view. Before, all morbid products, tumors, cancers, purulent collections, tubercles, gummas had been explained as arising in, or from, a hypothetical primitive blastema, itself exudative in nature. Now these were shown to be composed of living body cells, differing in various ways from the normal, exhibiting alterations both in form and function. With histological technique in its infancy, much was incomplete and misinterpretations were bound to occur, even as they do to-day.

Let me illustrate the accuracy of observation shown in the "Cellular Pathology" by quotations dealing with the subject of argyria, the deposit of silver pigment in the tissues. Every student of pathology now knows that argyriasis shows a selective affinity for the fibrillae of connective tissue. Silver is not deposited in epithelial structures, although it usually gains entrance to the body by passing through an epithelium. Note how clearly Virchow states these facts.

> We know that when any one takes salts of silver, they penetrate into the different tissues of his body. . . . A patient who had . . . received a solution of nitrate of silver as a lotion [for the eyes], very conscientiously employed the remedy . . . ; the result of which was that his conjunctiva

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[5] Schwalbe, J. Virchow-Bibliographie, 1843-1901. G. Reimer, Berlin, 1901. Pp. 183.

> assumed an intensely brown, nearly black appearance. The examination of a piece cut out of it showed that silver had been taken up into the parenchyma, and indeed in such a manner that the whole of the connective tissue had a slightly yellowish brown hue upon the surface, whilst in the deeper parts the deposition had taken place only in the fine elastic fibers of the connective tissue, the intervening parts, the proper basis-substance, being perfectly free. But deposits of an entirely similar nature take place also in more remote organs. Our collection contains a very rare preparation from the kidneys of a person who on account of epilepsy had taken nitrate of silver internally. In it may be seen the Malpighian bodies, in which the real secretion takes place, with a blackish blue coloring of the whole of the membrane of the coil of the vessels, limited to this part of the cortex, and appearing again, in a similar, though less marked form, only in the intertubular stroma of the medullary substance. . . . . The salts of silver do not deposit themselves in the lungs [when present in the circulating blood], but pass through them to be precipitated only when they reach the kidneys or the skin.

Taking second place in importance among the larger works of Virchow, is the three volume treatise on tumors, "Die Krankhaften Geschwülste." This was completed in the years 1863-1867. In it Virchow develops a systematic classification of neoplasms based largely upon their microscopical characteristics. Here the influence of his teacher, Johannes Müller, is evident. The terminology used by Virchow in this work still survives to a large degree.

Of the great array of lesser works, I can mention but a few groups. In the late forties Virchow, published a series of epoch-making papers on disturbances of the circulation. Here for the first time phlebitis, thrombosis, metastasis and embolism were clearly set forth. In fact, the term Embolia, or as we now say, embolism, was introduced by Virchow himself. Osler relates that in 1848, at the height of Virchow's political activity, he performed an autopsy upon a patient, said by Schönlein to have died from cerebral hemorrhage. Virchow found no hemorrhage, but succeeded in demonstrating an embolus blocking an important cerebral artery. Schönlein, who was present to see the outcome of his diagnosis, turned to Virchow and in a half-joking, half-vexed manner, said *Sie sehen auch überall Barricaden.* Other important monographs, papers and groups of papers were those dealing with calcium metastasis, pathological pigmentation, amyloid, leukaemia, chlorosis, phosphorus poisoning, syphilis, trichinosis, rickets, cretinism, encephalitis and peptic ulcer. The list might be much extended.

In 1847, Virchow with Reinhardt founded the *Archiv für pathologische Anatomie und Physiologie und für klinische Medicin.* This journal has been continued since that time, and constitutes the most important collection of original contributions to scientific medicine. After Reinhardt's death in 1852, Virchow carried the editorship alone for many years, so that even now one finds as many citations to this journal by the phrase "Virchow Archiv" as by its proper title. From 1851 to 1893 he was the joint editor, and from 1893 to 1901 the sole editor, of Canstatt's *Jahresbericht über die Leistungen und Fortschritte in der gesammten Medicin.* From 1850 to 1862, Virchow shared with Kölliker, Scherer and Scanzoni the editorship of the *Verhandlungen der physikalisch-medicinischen Gesellschaft in Würzburg.*

A list of Virchow's pupils would include most of the makers of medicine of the last fifty years. Scattered throughout the civilized world, they have from time to time brought together in *Festschriften* and memorial celebrations lists of names and collections of original contributions of which their old master may well have been proud. The *Festschrift* for his seventy-first birthday contributed by his former, and then acting, assistants in the Berlin Pathological Institute includes in its table of contents the names of v. Rechlinghausen, Klebs, Salkowski, Orth, Grawitz and Langerhans, among others, all of whom have had a great influence on the development of pathology and modern medicine. American medicine owes much to those who were under Virchow's tutelage in the last three decades of the nineteenth century.

Virchow was wrong. The cell is not the ultimate unit of life, but the methods of cellular pathology have grown no less important since he gave his great work to the world. The cell with its miscroscopically demonstrable content is still the morphological unit of life. Disease processes are still interpreted in the light of the cellular changes.

To Virchow we owe our conception of disease. Disease is not an entity, entering the body from without. Disease is life, life which deviates from the normal. The casual factor may reside within or may come from without in the form of trauma, infection, intoxication, or what not, but the cause is not the disease. The disease is the abnormal life of the body cells. The methods of modern medicine are therefore broadly biologic, and along this road of promise Rudolf Virchow pointed the way.

MEDICAL BIBLIOGRAPHY AND THE PERPETUATION OF ERROR

To the Editor:—The extent to which a scientific article should give bibliographic evidence of research in the literature on the part of its writer cannot be determined by rule. The character of the subject, the degree of familiarity with it possessed by the intended readers, the method of approach by other authors, and a dozen other factors will decide for the writer whether he should attempt a complete analysis of the literature of his subject, include a comprehensive annotated bibliography, append a complete author-subject list, content himself with citations of authorities, broadly summarize the literature without citations, or perchance ignore his predecessors entirely. In its proper setting, any one of these courses might be found satisfactory and sufficient; but the more limited the topic, the more precise its application, the more necessary does it become for the author to give evidence of familiarity with the literature of the subject concerning which he writes. He can best do this by such bibliographic apparatus as may be found necessary, for, to those expert in his own line, his thesis may exhibit abundant internal evidence of the possession of such familiarity and yet be judged inadequate and superficial through lack of external evidence when read by the inexpert. Thus it has come about that a criterion invariably applied to the written presentation of the results of a scientific investigation is whether or not it is accompanied by an adequate bibliography. One need not dip very far into current medical literature to discover why a real necessity for the application of this test exists.

As one corollary to this condition has been developed the use of coarse, bulky, undigested and unassimilated bibliography to give volume and dignity of appearance to an article altogether unworthy of such an appendage. If a bibliography is a good thing, insuring a hearing by a respectable audience, let us have a bibliography and that a long one.

It is a second corollary, however, which prompts the writing of this note. The author of a scientific communication, altogether sufficiently familiar with the literature of his subject, knowing that it has been abstracted from various angles by twenty or a hundred others before him, still feels that his paper must give external evidence of his familiarity. So he appends his bibliography and cites his authorities. But he avails himself of the abstracts and bibliographies of one or more of his predecessors and does not go to the original sources. He may not realize that some of his forebears have done likewise, and hence the perpetuations of error, misquotations, false translations and, above all, incorrect references, passed along from one to another, unchallenged and uncorrected.

If an example is needed (let us hasten to state that in quoting one no personal application is intended, and apologies are tendered), the adventure in bibliographic research here narrated may serve.

In an article on "Primary Tuberculosis of the Faucial Tonsils in Children" (*Journal of Pathology and Bacteriology* **21**:248-266, 1916-1917) Mitchell writes:

> Orth (1879[30]) seems to have been the first to have recorded a case of primary affection of the tonsil. He found tuberculosis of the tonsils in children who had died of diphtheria, the lungs being free from tuberculosis.

The reference (30) cited is Orth, *Virchows Archiv,* Berlin, 1879, Bd. LXXVI, s. 222. This is found to be Orth's important paper on the experimental study of ingestion tuberculosis. Page 222, which is the sixth page of the article, details the results as observed in Dog 17, in which tuberculous lesions of the tonsils and base of the tongue were noted. There is no record on this, or the preceding or following pages, of the observation of primary tonsillar tuberculosis in children dying of diphtheria.

Mitchell had access to an article by Carmichael (*Proceedings of the Royal Society of Medicine* [Section for Diseases of Children] **3,** pt. 1, pp. 27-36, 1910), for the reference is found in his bibliography. In this article Carmichael writes:

> Orth seems to have been the first to have recorded a case of primary affection of the tonsil.

Carmichael's reference, as well as the diction, is identical with that just quoted from Mitchell, and, as we have just seen, refers the reader only to experimentally produced lesions in dogs.

Mitchell also refers to an article by Bandelier (*Beiträge zur Klinik der Tuberculose* **6**:1-44, 1906). On the eleventh page of this article, Bandelier thus refers to the work of Orth:

> (Translation) Orth, who was the first to observe primary tonsillar tuberculosis in children dying of diphtheria, and otherwise tuberculosis-free, was able to produce cervical node tuberculosis in puppies by feeding tuberculous material, in one instance with a macroscopically demonstrable primary tonsillar tuberculosis.

In his bibliography, Bandelier gives the same reference as Mitchell and Carmichael, but without mentioning the page pertaining to Dog 17, to the article by Orth in *Virchows Archiv für pathologische Anatomie,* which, as we have just seen, is a proper citation only for the second part of his abstract. As a reference, it is but a half truth at the best. The whole truth must be sought a step farther back.

Mitchell and Bandelier both refer to a bulky article by Friedmann (of serum therapy fame) which is found in the *Beiträge zur pathologischen Anatomie* **28**:66-135, 1900. Here we find a possible source of the faulty references of Mitchell, Carmichael and Bandelier.

> (Translation) Orth[13 14] found tuberculosis of the cervical nodes in seven out of nine puppies fed tuberculous material; in part of the animals specific ulcers of the mouth were met, and once tuberculous lesions of the tonsils. Further, the same author has found tubercles, without pulmonary tuberculosis, in the tonsils of children dying of diphtheria.

The two references given are true and complete. The thirteenth is to the article in *Virchows Archiv* and the fourteenth to Orth's "Lehrbuch der speciellen pathologischen Anatomie," on page 663 of which (1887 edition) the observation of primary tuberculosis in children dying of diphtheria is noted. This is the probable source, and the sequence given above, a possible pedigree, for Mitchell's false reference. Whether other generations were present in the chain and to what extent collateral inheritance took place has not been investigated.

Friedmann's method of giving double references without specifying the application of each was awkward, but would have caused no trouble had those desiring to present an abstracted bibliography of tonsillar tuberculosis consulted the original sources. Medical literature is strewn with bibliographic items similarly unverified, giving the impression of abundant and accurate library research on superficial examination, but proving very disappointing when their verification is attempted. The moral is obvious.

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